NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Post-Authorisation Active Safety Surveillance Program Among Patients Treated With Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Juvenile Psoriatic Arthritis (PsA) Within the United Kingdom (UK) Juvenile Idiopathic Arthritis (JIA) Biologics Register
Protocol number	A3921409
Protocol version identifier	1.0
Date	03 May 2023
EU Post Authorization Study (PAS) register number	Pending (prior to start of data collection)
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-004; 014-015
Procedure number	EMEA/H/C/004214/X/0024/G
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	**Research question:** What are the incidence rates (IRs) of safety events of special interest in patients with pJIA or Juvenile PsA in the UK JIA Biologics Register who are treated with tofacitinib and with approved

	biological disease-modifying antirheumatic drugs (bDMARDs)? **Primary objective:** To estimate the post-approval real-world IR of the following outcomes of interest among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort): - Venous thromboembolism - Serious infections and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections) - All malignancies combined [excluding nonmelanoma skin cancer (NMSC)] - Lymphoma (examined as a separate outcome) - Lung cancer (examined as a separate outcome) **Secondary objective 1:** To estimate the post-approval real-world IR of the following outcomes of interest among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort): - Gastrointestinal perforations - Major adverse cardiac events (including MI) - Hypersensitivity - Growth or development disturbances - Fractures - Progressive multifocal leukoencephalopathy (PML) - All-cause mortality

	- Herpes zoster (HZ) reactivation - NMSC - Interstitial lung disease **<u>Secondary objective 2:</u>** To compare the risk of outcomes of interest listed under the primary objective and the secondary objective 1 among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort). This comparison will be restricted to the outcomes of interest, where there are adequate data.
Country(-ies) of study	United Kingdom
Author	Sampada Gandhi Sampada.Gandhi@pfizer.com Director, Epidemiology, Safety Surveillance Research Scientist Pfizer, Inc. 100 Route 206 N Pfizer Way Peapack, NJ 07977

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Pfizer Europe MA EEIG
MAH contact person	Anne Lenihan Anne.Lenihan@pfizer.com Pfizer Ltd Walton Oaks Dorking Road Walton-on-the-Hill Surrey KT20 7NS United Kingdom

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS....5
2. LIST OF ABBREVIATIONS....7
3. RESPONSIBLE PARTIES....11
4. ABSTRACT....12
5. AMENDMENTS AND UPDATES....16
6. MILESTONES....17
7. RATIONALE AND BACKGROUND....17
8. RESEARCH QUESTION AND OBJECTIVES....18
9. RESEARCH METHODS....19
9.1. Study design....19
9.2. Setting....19
9.2.1. Inclusion criteria....20
9.2.1.1. Patients with pJIA or juvenile PsA initiating tofacitinib (Tofacitinib cohort)....20
9.2.1.2. Patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort)....20
9.2.2. Exclusion criteria....21
9.3. Variables....21
9.3.1. Baseline characteristics....21
9.3.1.1. Demographic characteristics....21
9.3.1.2. Calendar year of cohort entry....21
9.3.1.3. Disease activity....21
9.3.1.4. Subtype of JIA (ILAR classification)....21
9.3.1.5. Age at JIA diagnosis and duration of JIA....22
9.3.1.6. Prior JIA therapy....22
9.3.1.7. Comorbidities....22
9.3.1.8. Concomitant medications....22
9.3.1.9. Body mass index (BMI)....22
9.3.1.10. Vaccination status at baseline and during follow-up....22
9.3.2. Exposure ascertainment....23
9.3.3. Follow-up of patients....23
9.3.4. Outcomes of interest....23

9.4. Data sources 25
9.5. Study size 25
9.6. Data management 32
9.7. Data analysis 32
9.7.1. All outcomes of interest except all malignancies combined (excluding NMSC), NMSC, lymphoma, and lung cancer 33
9.7.2. Nonmelanoma skin cancer (NMSC), all malignancies combined excluding NMSC, lymphoma, and lung cancer 34
9.8. Quality control 35
9.9. Limitations of the research methods 35
9.10. Other aspects 37
10. PROTECTION OF HUMAN SUBJECTS 37
10.1. Patient information 37
10.2. Patient consent 37
10.3. Institutional review board (IRB)/Independent ethics committee (IEC) 37
10.4. Ethical conduct of the study 37
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 37
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 37
13. REFERENCES 38
14. LIST OF TABLES 40
15. LIST OF FIGURES 40
ANNEX 1. LIST OF STAND ALONE DOCUMENTS 40
ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS 44
ANNEX 3. ADDITIONAL INFORMATION 51

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College for Rheumatology
AE	adverse event
AJC	active joint count
BCRD	Biologics for Children with Rheumatic Diseases
bDMARDs	biological disease-modifying antirheumatic drugs
BID	twice daily
BiKeR	German Biologics in Pediatric Rheumatology Registry
BMI	body mass index
BSG	Biologic Studies Group
BSPAR-ETN	British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
COV	Core Outcome Variables
CRF	case report form
CRP	C-reactive protein
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
DALY	disability-adjusted life year
DMARDs	disease-modifying antirheumatic drugs
eCRF	Electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GI	gastrointestinal
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HIB	Haemophilus influenzae type b
HR	hazard ratio
HRQoL	health-related quality of life
HZ	Herpes Zoster
IEC	Independent Ethics Committee
ILAR	International League of Associations for Rheumatology
IR	incidence rate
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JADAS	Juvenile Arthritis Disease Activity
JAK	Janus Kinase
JIA	juvenile idiopathic arthritis
JuMBO	Juvenile Arthritis Methotrexate/Biologics long-term Observation
LJC	limited joint count
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities

MI	myocardial infarction
MTX	methotrexate
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
NMSC	nonmelanoma skin cancer
NNH	numbers needed to harm
PASS	Post-authorization Safety Study
pcJIA	polyarticular-course JIA
pJIA	polyarticular juvenile idiopathic arthritis
PML	progressive multifocal leukoencephalopathy
PsA	psoriatic arthritis
PY	person-year
QALY	quality-adjusted life year
RA	rheumatoid arthritis
RF	rheumatoid factor
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDS	standard deviation scores
sJIA	systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
TNF	tumor necrosis factor
UC	ulcerative colitis

UK	United Kingdom
VAS	visual analogue scores
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Sampada Gandhi, MD, PhD	Director, Epidemiology Safety Surveillance Research Scientist	Pfizer, Inc.	100 Route 206 N Pfizer Way, Peapack, New Jersey 07977
Kimme Hyrich, MD, PhD, FRCPC	Professor of Epidemiology and Consultant Rheumatologist	The University of Manchester Centre for Musculoskeletal Research	2nd Floor Stopford Building, Oxford Road, Manchester, M13 9PL United Kingdom

4. ABSTRACT

- Title: Post-Authorisation Active Safety Surveillance Program Among Patients Treated With Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Juvenile Psoriatic Arthritis (PsA) Within the United Kingdom (UK) Juvenile Idiopathic Arthritis (JIA) Biologics Register

  Version: 1.0

  Date: 03 May 2023

  Author: Sampada Gandhi, Pfizer, Inc.

- Rationale and background: 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. 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. Tofacitinib (Xeljanz®) is an oral Janus Kinase (JAK) inhibitor approved in the European Union (EU) in adult populations for the treatment of moderate to severe rheumatoid arthritis (RA), active PsA, and moderate to severe ulcerative colitis (UC). The safety of tofacitinib has been evaluated in 251 JIA patients aged 2 to <18 years treated with tofacitinib 5 mg twice daily (BID) or weight based equivalent of oral solution and tofacitinib was shown to be safe and well-tolerated. The understanding of tofacitinib safety 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 5 mg BID. The safety profile of tofacitinib in the JIA clinical program was consistent with that of the adult RA clinical program, and no new safety risks were identified. The important identified and potential risks associated with use of tofacitinib listed in the Risk Management Plan (RMP) include (but not limited to): venous thromboembolism, serious infections (including tuberculosis), herpes zoster or HZ, malignancy [excluding NMSC], NMSC, lymphoma, lung cancer, interstitial lung disease, fractures, gastrointestinal perforations, all-cause mortality, PML, myocardial infarction (MI), and cardiovascular risk (excluding MI). Within the JIA population, additional events of interest include growth or development disturbances, and response to vaccination. Furthermore, drug hypersensitivity is considered as an identified risk and listed in the Summary of Product Characteristics (SmPC) but does not meet the criteria to be included in the RMP. As part of the tofacitinib pharmacovigilance plan, Pfizer will implement a post approval, active surveillance study of patients with pJIA or juvenile PsA initiating tofacitinib and those treated with approved bDMARDs using prospectively collected data included in the UK JIA Biologics Register to actively monitor the safety events of interest in the post-approval real-world setting, including events associated with long-term use.

- Research question: What are the IRs of safety events of special interest in patients with pJIA or juvenile PsA in the UK JIA Biologics Register who are treated with tofacitinib and with approved bDMARDs?

- Objectives:

  Primary objective: To estimate the post-approval real-world IR of the following outcomes of interest among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib

cohort) and among patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort):

- Venous thromboembolism
- Serious infections and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections)
- All malignancies combined (excluding NMSC)
- Lymphoma (examined as a separate outcome)
- Lung cancer (examined as a separate outcome

Secondary objective 1: To estimate the post-approval real-world IR of the following outcomes of interest among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and among patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort):

- Gastrointestinal perforations
- Major adverse cardiac events (including MI)
- Hypersensitivity
- Growth or development disturbances
- Fractures
- PML
- All-cause mortality
- HZ reactivation
- NMSC
- Interstitial lung disease

Secondary objective 2: To compare the risk of outcomes of interest listed under the primary objective and the secondary objective 1 among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort). This comparison will be restricted to the outcomes of interest, where there are adequate data.

- Study design: This is an active surveillance study utilizing data from the UK JIA Biologics Register, which consists of two parallel national biologic registers for children and young people with JIA within the UK; the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN), established in 2004, and the Biologics for Children with Rheumatic Diseases (BCRD) study, established in 2010 focusing on non-etanercept biologics and other targeted therapies including JAK inhibitors**.**

- Population: The study population will comprise all patients with pJIA or juvenile PsA enrolled within the UK JIA Biologics Register who receive tofacitinib following product availability in the UK since 07 April 2022 through 01 July 2029. One comparator cohort comprised of patients with pJIA or juvenile PsA treated with approved bDMARDs (etanercept being the most prevalent bDMARD used within the UK registers) and identified from 01 January 2010 through 01 July 2029 will be assembled to provide context for rates observed among patients treated with tofacitinib.

- Variables: Key variables include baseline characteristics such as patient demographics, disease activity, comorbidities, subtype of JIA, prior JIA therapy and concomitant medications. Exposure will be defined as tofacitinib treatment and bDMARD treatment. The outcomes of interest are as described under the objective.

- Data sources: The UK JIA Biologic Register consists of two parallel national biologic registers for children and young people with JIA within the UK; BSPAR-ETN established in 2004, and the BCRD study established in 2010 focusing on non-etanercept biologics and other targeted therapies including JAK inhibitors. In parallel, both studies also have recruited a comparison arm of children and young people starting methotrexate (MTX). One of the aims of the register is to assess safety of biologic and targeted synthetic therapies in children and young people with JIA. Although not mandatory, recruitment is recommended for all patients starting a biologic therapy and children have been recruited from almost every centre treating children with JIA in the UK. As of 09 November 2020, there were 1,096 children and young people recruited starting MTX, and 2,436 recruited starting a biologic/targeted synthetic therapy across all JIA International League of Associations for Rheumatology (ILAR) indications.

- Study size: This is a descriptive study without pre specified hypotheses. All eligible patients enrolled in the UK JIA Biologics Register following product availability in the UK since 07 April 2022 through 01 July 2029 will be included in the tofacitinib cohort, with no upper limit on the sample size. The projected number of children starting tofacitinib in the UK is currently unknown and will be highly dependent on a number of factors including the approvals of drug by the UK National Institute for Health and Clinical Excellence (NICE) and the use of the drug by paediatric rheumatologists in the UK. As the UK JIA Register is an observational study, it cannot influence the prescribing of the drug, but the register strives to capture all children starting new targeted therapies. A comparison cohort of approximately 1,100 children with pJIA or juvenile PsA starting with the approved bDMARDs who fulfil the inclusion/exclusion criteria and who have been recruited from 01 January 2010 to 01 July 2029 will also be included, with no upper limit on sample size (recruitment is ongoing). These include approximately 500 children starting etanercept, 400 adalimumab, 90 infliximab, 80 tocilizumab, and 30 abatacept recruited between 01 January 2010 and 01 October 2021 for active pJIA and PsA. These children remain under active follow-up in the register.

- Data analysis: Descriptive analyses will be performed to summarize baseline demographic and clinical characteristics of the tofacitinib and the comparison cohorts. Crude incidence rates per 100 person-years (PY) and 95% confidence intervals (CIs) of safety events of interest will be estimated in both cohorts, where only the first occurrence of each outcome of interest will be counted. In addition to estimating the crude IRs, a comparative analysis will be conducted to examine the risk of the outcomes of interest among patients from the tofacitinib cohort compared to the patients from the comparator cohort adjusting for confounding by baseline characteristics. For the outcomes of interest, where there are adequate data to compare the risk between tofacitinib cohort and comparator cohort, multivariable Cox proportional hazards models will be fit to compare risk of the outcome of interest between the tofacitinib cohort and the comparator cohort.

- Milestones:

  Protocol submission: 07 February 2022

  Start of data collection (planned date for starting data extraction from the registry data source for the purpose of interim study report): 01 March 2026

  Interim report: 30 August 2026

  End of data collection (planned date on which the analytical dataset is completely available): 01 November 2030

  Final study report: 01 May 2031

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	Pending (prior to start of data collection)
Start of data collection*	01 March 2026
Interim report	30 August 2026
End of data collection**	01 November 2030
Final study report	01 May 2031

* The start of data collection corresponds to the date of start of data extraction for the purposes of the primary analysis. The primary analysis refers to the interim analysis conducted at the time of interim study report.

** The end of data collection corresponds to the planned date on which the analytical dataset is completely available.

7. RATIONALE AND BACKGROUND

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 ILAR has classified JIA into 7 distinguishable subtypes as follows: rheumatoid factor (RF)+ polyarthritis, RF- polyarthritis, oligoarthritis (persistent and extended), systemic JIA (sJIA), juvenile 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.[2] A systematic review including 43 articles, 33 concerning incidence data and 29 concerning prevalence data reported incidence rates of JIA varying from 1.6 to 23 per 100,000 and prevalence ranging from 3.8 to 400 per 100,000.[3] This review included studies conducted in Europe (24 articles), North America (13 articles), Latin America (2 articles), Middle East (2 articles), Asia (1 article) and Australia (1 article) and JIA was defined using the American College for Rheumatology (ACR), the European League Against Rheumatism (EULAR) and the ILAR classification.

Tofacitinib (Xeljanz®) is an oral JAK inhibitor approved in the EU in adult populations for the treatment of moderate to severe RA, active PsA, and moderate to severe UC. The safety of tofacitinib has been evaluated in 251 JIA patients aged 2 to <18 years treated with tofacitinib 5 mg BID or weight based equivalent of oral solution and tofacitinib was shown to be safe and well-tolerated. The understanding of tofacitinib safety 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 5 mg BID. The safety profile of tofacitinib in the JIA clinical program was consistent with that of the adult RA clinical program, and no new safety risks were identified. Tofacitinib was approved in the UK in September 2021 by the European Medicines Agency (EMA) for pJIA defined

as RF+, polyarthritis, RF- polyarthritis, and extended oligoarthritis and for juvenile PsA. Therefore, consistent with the SmPC, patients with pJIA or juvenile PsA subtypes will be included in this study.

The important identified and potential risks associated with use of tofacitinib listed in the RMP include (but not limited to): venous thromboembolism, serious infections (including tuberculosis), herpes zoster or HZ, malignancy (excluding NMSC) and NMSC, lymphoma, lung cancer, fractures, interstitial lung disease, gastrointestinal perforations, all-cause mortality, PML, MI and cardiovascular risk (excluding MI). Within the JIA population, additional events of interest include growth or development disturbances, and response to vaccination. Drug hypersensitivity is considered as an identified risk and listed in the SmPC but does not meet the criteria to be included in the RMP.

Active surveillance studies can estimate incidence rates of safety events of interest overall and within strata of disease severity, treatment history, and other concomitant therapy in tofacitinib-treated JIA patients in the post-approval real-world setting and in JIA patients treated with approved bDMARDs to provide context for rates observed among patients treated with tofacitinib. Therefore, as part of the tofacitinib pharmacovigilance plan, three non-interventional studies will be conducted using data from four existing JIA registries, namely, the German Biologics in Pediatric Rheumatology Registry (BiKeR), Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) registry, which is a follow-up registry of JIA patients from the BiKeR registry into adulthood, the Swedish JIA Clinical Register/Nationwide Swedish healthcare registers, and the UK JIA Biologics Register, to actively monitor the safety events of interest in tofacitinib treated JIA patients in the post-approval real-world setting, including events associated with long-term use. Three separate study protocols, one each for the UK JIA biologics Register and the nationwide Swedish healthcare registers and a combined protocol using BiKeR and JuMBO registries have been developed.

This study protocol describes the details of the active surveillance study using prospective data included in the UK JIA Biologics Register. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a Category 3 commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: What are the IR of safety events of interest in patients with pJIA or juvenile PsA in the UK JIA Biologics Register who are treated with tofacitinib and with approved bDMARDs?

Objectives:

Primary objective: To estimate the post-approval real-world incidence rate of the following outcomes of interest among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort):

- Venous thromboembolism
- Serious infections and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections)
- All malignancies combined (excluding NMSC)

- Lymphoma (examined as a separate outcome)
- Lung cancer (examined as a separate outcome)

Secondary objective 1:

To estimate the post-approval real-world IR of the following outcomes of interest among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort):

- Gastrointestinal perforations
- Major adverse cardiac events (including MI)
- Hypersensitivity
- Growth or development disturbances
- Fractures
- PML
- All-cause mortality
- HZ reactivation
- NMSC
- Interstitial lung disease

Secondary objective 2:

To compare the risk of outcomes of interest listed under the primary objective and the secondary objective 1 among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort). This comparison will be restricted to the outcomes of interest, where there are adequate data.

9. RESEARCH METHODS

9.1. Study design

This is an 8-year active surveillance, secondary data collection study of patients with pJIA or juvenile PsA using data from the UK JIA Biologics Register during a period of 2022 to 2030 for the tofacitinib cohort and during a period of 2010 to 2030 for the comparator cohort.

Incidence rates of safety events of interest will be estimated in patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort) with 95% CI and reported as descriptive analyses. No a priori hypotheses will be specified. For the outcomes of interest, where there are adequate data to compare the risk between tofacitinib cohort and comparator cohort, multivariable Cox proportional hazards models will be fit to compare risk of the outcome of interest between the tofacitinib cohort and the comparator cohort.

9.2. Setting

The study period will be defined from 07 April 2022 (corresponding to tofacitinib availability in the UK) to 01 July 2030 for the tofacitinib cohort and from 01 January 2010 to 01 July 2030 for the comparator cohort. This study is set within the UK JIA Biologics Register. Data from the UK JIA Biologics Register has contributed to a range of publications focusing on real-world biologic

treatment effectiveness and safety.[4, 5, 6, 7] Historically and due to the nature of prior funding, data on children with JIA starting biologics, targeted therapies and MTX were captured in 2 parallel but identical studies, both based at The University of Manchester. The BSPAR Etanercept cohort study collects data from children starting etanercept or methotrexate. The BCRD Study collects data from children starting non-etanercept bDMARDS, including other tumor necrosis factor (TNF) inhibitors such as adalimumab, JAK inhibitors or MTX. Both studies operate under the single banner of the UK JIA Biologics Register. Patients can contribute data to both studies and data captured using identical methods from the same hospitals are pooled for analyses. A full copy of all study documentation, protocols and case report forms (CRF) can be downloaded from: https://sites.manchester.ac.uk/bcrdbspar/information-for-healthcare-professionals/.

9.2.1. Inclusion criteria

The active surveillance population includes patients with pJIA or juvenile PsA enrolled in the UK JIA Biologics Register who are newly treated with tofacitinib following UK approval (September 2021) and launch of the product in the UK (product is available in the UK since 07 April 2022). For contextualization purposes, the study population will also include a comparator cohort of children with pJIA and juvenile PsA starting with approved bDMARDs recruited since 01 January 2010 to 01 July 2029 identified from the existing register (recruitment is ongoing and these children remain under active follow-up in the register). The UK JIA Biologics Register is approved under the UK Health Research Authority and all participants give written informed consent for data to be captured within the register. However, no additional ethical approvals or consent are required for the secondary analyses of data, sharing of anonymised data or sharing of aggregated results, including this PASS study. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

9.2.1.1. Patients with pJIA or juvenile PsA initiating tofacitinib (Tofacitinib cohort)

1. Rheumatologist diagnosis of pJIA defined as extended oligoarthritis, polyarthritis (RF+), or polyarthritis (RF-) or a diagnosis of juvenile PsA

2. Patients younger than 16 years at diagnosis of pJIA or juvenile PsA

3. Patients aged 2-17 years at tofacitinib initiation

4. Initiation of tofacitinib as a monotherapy or in combination with MTX following product availability on 07 April 2022 through 01 July 2029 and as captured in the UK JIA Biologics Register

9.2.1.2. Patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort)

1. Diagnosis of pJIA defined as extended oligoarthritis, Polyarthritis (RF+), or Polyarthritis (RF-) or juvenile PsA by a rheumatologist

2. Patients younger than 16 years at diagnosis of pJIA or juvenile PsA

3. Patients aged 2-17 years at initiation of any bDMARD approved for pJIA or juvenile PsA treatment in UK (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). For example, a patient starting etanercept for the first time during the period of 01 January 2010 to 01 July 2029 will be eligible regardless of this patient's prior use of another bDMARD, for example tocilizumab.

4. Patients initiating a bDMARD as a monotherapy or in combination with MTX during the study period from 01 January 2010 to 01 July 2029 and as captured in the UK JIA Biologics Register

9.2.2. Exclusion criteria

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

Tofacitinib cohort

1) Concurrent use of bDMARDs

Comparator cohort

1. Patients with prior use of tofacitinib

2. Concurrent use of more than 1 bDMARD

9.3. Variables

9.3.1. Baseline characteristics

Baseline data will be captured at the start of the index therapy (tofacitinib or bDMARDs). Index date will be defined as the date of first prescription for tofacitinib and bDMARDs in the tofacitinib and the comparator cohort, respectively.

9.3.1.1. Demographic characteristics

Data captured in the register includes the following: age at cohort entry, sex, race (white, non-white), and geographic region (England, Wales, Scotland, Northern Ireland).

9.3.1.2. Calendar year of cohort entry

9.3.1.3. Disease activity

Detail of JIA Core Outcome Variables (COVs) are captured at baseline and include active joint count (AJC), limited joint count (LJC), erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP), Physicians Global Assessment of disease activity, Patient (or parent) Global Assessment of well-being, pain visual analogue scores (VAS), and Childhood Health Assessment Questionnaire (CHAQ). The Juvenile Arthritis Disease Activity (JADAS) score is calculated as a sum of the AJC, physician global, patient global and a normalized ESR and the score ranges from 0-10.

9.3.1.4. Subtype of JIA (ILAR classification)

- Polyarthritis RF-
- Polyarthritis RF+

- Oligoarthritis extended
- Juvenile PsA

9.3.1.5. Age at JIA diagnosis and duration of JIA

Data on age at JIA diagnosis and duration of JIA will be reported.

9.3.1.6. Prior JIA therapy

Data on prior JIA therapy including systemic glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and bDMARDs will be reported.

9.3.1.7. Comorbidities

Data on comorbidities such as uveitis, atopy (eczema, asthma) will be reported.

9.3.1.8. Concomitant medications

Data on concomitant medications such as MTX, systemic glucocorticoids and key non-JIA therapies (e.g., therapies used in the treatment of comorbidities) will be reported.

9.3.1.9. Body mass index (BMI)

Baseline BMI will be calculated based on available height and weight information prior to the index date.

9.3.1.10. Vaccination status at baseline and during follow-up

The UK JIA Biologics Register captures details on routine childhood vaccinations and it is assumed that children have received all vaccinations unless it is specifically documented that they have not at baseline and during the follow-up period (based on the UK standard vaccination protocol in Table 1). The specific dates of vaccination are not recorded, but an ethical amendment will be submitted to add date and details of any vaccinations received after cohort entry.

Table 1. Information on vaccinations captured in the UK JIA Biologics Register*

Age	Vaccination
2 months	1st diphtheria, tetanus, pertussis, polio, haemophilus influenzae type b (hib)
	1st pneumococcal infection
	1st rotavirus
3 months	2nd diptheria, tetanus, pertussis, polio, hib
	1st meningitis C
	2nd rotavirus
4 months	3rd diptheria, tetanus, pertussis, polio, hib
	2nd pneumococcal infection
12-13 months	1st measles, mumps and rubella
	Booster: pneumococcal infection
	Booster: hib, meningitis C
Pre-school	Booster: diphtheria, tetanus, pertussis, polio
	2nd measles, mumps and rubella

12-13 years	1st, 2nd and 3rd human papilloma virus
13-18 years	Booster: diptheria, tetanus, polio
Other	Annual Influenza
	Pneumococcal Vaccine

* Subject to change as per UK National Guidance

9.3.2. Exposure ascertainment

Exposure to tofacitinib, approved bDMARDs and MTX will be identified through direct hospital source report into the online eCRF available at https://sites.manchester.ac.uk/bcrdbspar/information-for-healthcare-professionals/. The exposure will be captured in the eCRF by physicians at each visit. Each exposure drug, ie, tofacitinib and DMARD has its own drug code, which will be selected by the clinical team and will be captured by the system and stored in the database. Duration of exposure to tofacitinib and approved bDMARDs will be calculated from the start and end date of each respective exposure drug. In addition, dose and frequency of exposure treatments of tofacitinib and approved bDMARDs will be described.

Exposure to concurrent MTX will be identified using the start and end dates from the registries. However, dose and duration of concurrent MTX will not be described, but the information will only be used to identify whether patients received tofacitinib or comparator treatment as monotherapy or in combination with MTX on the index date.

9.3.3. Follow-up of patients

Follow-up data is captured directly from the treating rheumatology team at set intervals from 1st date of registration in the UK JIA biologics register. These are at 6 months, 12 months and annually thereafter. At each follow-up the local team extract data and submit it to the UK JIA biologics Register using the online CRF. Follow-up data includes changes to anti-rheumatic medications, including any changes in therapy and reasons, and occurrence of safety events of interest.

For the analysis, patients will be followed from the index date until the earliest of first occurrence of each outcome of interest, death, last recorded study follow-up, emigration from UK, and end of study period (ie, 01 July 2030) treated as censoring events. For each outcome of interest, occurrence of that outcome will result in censoring. However, occurrence of another outcome 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 of interest

The following outcomes of interest will be examined in the interim and final study report. All outcomes, with the exception of growth or development disturbances, will be identified using the

Medical Dictionary for Regulatory Activities (MedDRA) codes. Please see Annex 1 for relevant MedDRA codes.

- Venous thromboembolism
- Serious infections and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections)
- All malignancies combined (excluding NMSC)
- Lymphoma (examined as a separate outcome)
- Lung cancer (examined as a separate outcome)
- Gastrointestinal perforations
- Major adverse cardiac events (including MI)
- Hypersensitivity
- Growth or development disturbances:

  These will be assessed by examining height velocity z-score and BMI z-scores to evaluate growth disturbances and weight disturbances, respectively.

  - Height velocity z-scores: 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; z-score will be treated as a continuous variable and z-score and z-score values of < -2 standard deviations scores (SDS) as well as >+2 SDS (ie, more than two standard deviations below or above the mean) will be considered as abnormal.[8, 9,10] 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.

  - BMI z-scores: In addition to BMI calculated at baseline, BMI z-scores will be calculated based on annual BMI measurements.

- Fractures
- PML
- All-cause mortality

- HZ reactivation
- NMSC
- Interstitial lung disease

This list may be extended with a reasonable number of additional sub-diagnoses or new health related outcomes as agreed by UK JIA biologics Register and Sponsor before the interim analysis and final study report. These decisions will be made prior to initiation of analyses and documented in a statistical analysis plan (SAP) kept on file by Sponsor.

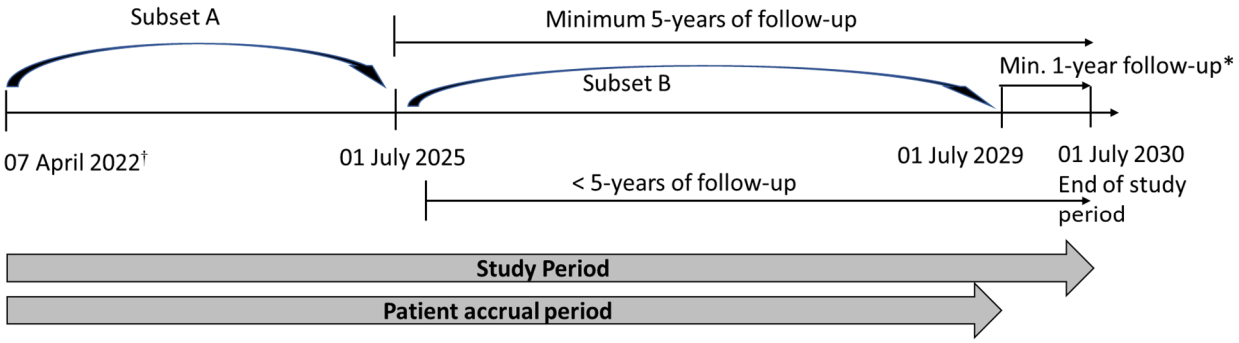
9.4. Data sources

This study utilizes existing data captured within the UK JIA Biologics Register. As of 09 November 2020, there were 1,096 children and young people recruited starting MTX, and 2,436 recruited starting a biologic/targeted synthetic therapy across all JIA ILAR indications. Relevant to this study, the register includes 500 children starting etanercept, 400 adalimumab, 90 infliximab, 80 tocilizumab and 30 abatacept recruited between 01 January 2010 and 01 October 2021 with active pJIA and juvenile PsA. These children remain under active follow-up at this time and will be followed until the UK JIA Biologics Register is active.

9.5. Study size

This is a descriptive study without pre specified hypotheses. All eligible patients enrolled in the UK JIA Biologics Register following UK approval (September 2021) and product availability in the UK since 07 April 2022 through 01 July 2029 will be included in tofacitinib cohort, with no upper limit on the sample size. The projected number of children starting tofacitinib in the UK is currently unknown and will be highly dependent on a number of factors including the approvals of drug by the UK NICE and the use of the drug by paediatric rheumatologists. As the UK JIA Register is an observational study, it cannot influence the prescribing of the drug, but the register strives to capture all children starting new targeted therapies. A comparison cohort of approximately 1,100 children with pJIA and juvenile PsA starting with the approved bDMARDs who fulfil the inclusion/exclusion criteria and who have been recruited since 01 January 2010 will also be included, with no upper limit on sample size (recruitment is ongoing).

Figure 1. Follow-up times for patients based on the date of initiation of tofacitinib



*A minimum of 1-year follow-up will be included for ALL patients in the study.
† Product availability date for the UK is 07 April 2022. Comparator cohort will include all patients during a period of 01 January 2010 until 01 July 2029 (patient accrual period for the comparator cohort is not shown in this figure).

As shown in Figure 1, of the total patients included in the study, a subset of eligible patients who initiate tofacitinib (or approved bDMARD) starting from 07 April 2022 (or 01 January 2010) through 01 July 2025 (Subset A) will have an opportunity to contribute to a minimum follow-up period of 5 years until the end of the study period (ie, 01 July 2030). Of these, some patients will have a follow-up greater than 5 years, for example, a patient who initiates tofacitinib or approved bDMARD on 01 July 2024 will be followed up for a period of 6 years until 01 July 2030. It should be noted that patients who initiate tofacitinib or approved bDMARD after 01 July 2025 (Subset B) will have an opportunity to contribute to a follow-up period of less than 5 years in the study.

Sample size is based on estimating precision for IRs (ie, number of patients with event per 100 PY) for outcomes of interest. It is expected to include approximately 250 patients in the tofacitinib cohort and a minimum of 750 patients in the comparator cohort. Even though the follow-up time for each patient will vary as described above and a subset of patients will have a minimum 5-years of follow-up, it is an assumption that the average follow up time per patient will range from 4.1 to 5.1 years, resulting in a total of 1,025 to 1,275 PYs and 3,075 to 3,825 PYs in the tofacitinib cohort and the comparator cohort, respectively. Further, based on published studies in JIA patients, it is assumed that the IRs of outcomes of interest range from 0.005 to 1 per 100 PYs in both cohorts of interest.[11, 12, 13, 14, 15, 16, 17, 18] Precision estimates in terms of the 95% CI for the IRs for various combinations of IRs and PYs are provided in Table 2.

Table 2. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and person-years

Assumed Total PY	Assumed IR (per 100 PY)	Lower Limit of 95% CI for IR (per 100 PY)	Upper Limit of 95% CI for IR (per 100 PY)
Tofacitinib Cohort			
500	0.005	0.00	0.74
500	0.010	0.00	0.74

Table 2. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and person-years

Assumed Total PY	Assumed IR (per 100 PY)	Lower Limit of 95% CI for IR (per 100 PY)	Upper Limit of 95% CI for IR (per 100 PY)
500	0.050	0.00	0.74
500	0.100	0.01	1.11
500	0.500	0.12	1.75
500	1.000	0.32	2.33
750	0.005	0.00	0.49
750	0.010	0.00	0.49
750	0.050	0.00	0.49
750	0.100	0.00	0.74
750	0.500	0.15	1.37
750	1.000	0.46	2.10
1000	0.005	0.00	0.37
1000	0.010	0.00	0.37
1000	0.050	0.00	0.56
1000	0.100	0.00	0.56
1000	0.500	0.16	1.17
1000	1.000	0.48	1.84
1025	0.005	0.00	0.36
1025	0.010	0.00	0.36
1025	0.050	0.00	0.54
1025	0.100	0.00	0.54
1025	0.500	0.16	1.14
1025	1.000	0.47	1.79
1275	0.005	0.00	0.29
1275	0.010	0.00	0.29
1275	0.050	0.00	0.44
1275	0.100	0.00	0.44
1275	0.500	0.17	1.02
1275	1.000	0.54	1.74

Comparator Cohort

Table 2. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and person-years

Assumed Total PY	Assumed IR (per 100 PY)	Lower Limit of 95% CI for IR (per 100 PY)	Upper Limit of 95% CI for IR (per 100 PY)
2000	0.005	0.00	0.18
2000	0.010	0.00	0.18
2000	0.050	0.00	0.28
2000	0.100	0.01	0.36
2000	0.500	0.24	0.92
2000	1.000	0.61	1.54
2250	0.005	0.00	0.16
2250	0.010	0.00	0.16
2250	0.050	0.00	0.25
2250	0.100	0.01	0.32
2250	0.500	0.24	0.87
2250	1.000	0.65	1.53
2500	0.005	0.00	0.15
2500	0.010	0.00	0.15
2500	0.050	0.00	0.22
2500	0.100	0.02	0.35
2500	0.500	0.28	0.89
2500	1.000	0.65	1.48
3075	0.005	0.00	0.12
3075	0.010	0.00	0.12
3075	0.050	0.01	0.23
3075	0.100	0.02	0.29
3075	0.500	0.27	0.80
3075	1.000	0.68	1.43
3825	0.005	0.00	0.10
3825	0.010	0.00	0.10
3825	0.050	0.01	0.19
3825	0.100	0.03	0.27
3825	0.500	0.30	0.78

Table 2. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and person-years

Assumed Total PY	Assumed IR (per 100 PY)	Lower Limit of 95% CI for IR (per 100 PY)	Upper Limit of 95% CI for IR (per 100 PY)
3825	1.000	0.70	1.36

Abbreviations: IR=incidence rate; CI=confidence interval; PY=person-year

The minimum detectable hazard ratios (HR) comparing tofacitinib-treated patients versus comparator-treated patients are calculated for the different incidence rates and sample sizes (250 patients in the tofacitinib cohort and 750 patients in the comparator cohort) and presented in Table 3 below. The calculations make the following additional assumptions: (1) power = 80%, (2) 2-sided α = 0.05, (3) 8-year total study duration (7-years patient uniform accrual, and minimum 1-year follow-up from the last enrolled patient), and (4) 5% annual loss to follow up or treatment switch for all patients.

Table 3. Table 3. Minimum Detectable Hazard Ratios Comparing Tofacitinib-Treated Patients versus Comparator-Treated Patients with 80% Power, 2-sided α = 0.05, 8-Year Total Study Duration with 7 Years of Uniform Accrual, 5% Loss to Follow Up or Treatment Switch Per Year

Assumed IR (per 100 PY) for Comparator Cohort	Sample Size in Tofacitinib Cohort	Sample Size in Comparator Cohort	Hazard Ratio
0.005†	250	750	>14*
0.01†	250	750	>14*
0.05†	250	750	11.54
0.08†	250	750	8.65
0.09†	250	750	8.03
0.1§	250	750	7.74
0.5§	250	750	3.28
1.0¶	250	750	2.48

*Infeasible to calculate the exact value due to assumed low IR (expect zero events in both the Tofacitinib cohort and Comparator cohort for the scenarios).
IR=incidence rate; PY=person-year
† The observed IRs of malignancies in the comparator cohort as reported in Horne et al 2019, Bernatsky et al 2011, Nordstrom et al 2012, Barth et al 2017, Beukelman et al 2012, and Horneff et al 2016.
§ The observed IRs of herpes zoster infection in the comparator cohort as reported in Nimmrich et al 2015.
¶ The observed IRs of serious infections in the comparator cohort as reported in Aygun et al 2019.

Based on the information presented in Table 3, a study with a sample size of 250 patients in the tofacitinib cohort and 750 patients in the comparator cohort would detect a HR no less than 3.28 and 7.74 (tofacitinb versus comparator) for an IR of 0.5 and 0.1 per 100 PY in the comparator cohort,

respectively, where the IRs of 0.5 and 0.1 per 100 PY represent a background incidence of herpes zoster infection in JIA patients [17]. Similarly, a study with a sample size of 250 patients in the tofacitinib cohort and 750 patients in the comparator cohort would detect a HR no less than 2.48 (tofacitinb versus comparator) for an IR of 1.0 per 100 PY in the comparator cohort, where the IR of 1.0 per 100 PY represents a background incidence of serious infections in JIA patients.[18] Lastly, the background IRs of malignancies in JIA patients range from 0.005 to 0.09 per 100 PY.[11, 12, 13, 14, 15, 16] A study with a sample size of 250 patients in the tofacitinib cohort and 750 patients in the comparator cohort would detect a HR no less than >14 (tofacitinb versus comparator) for an IR of 0.005 per 100 PY in the comparator cohort, respectively, where the IR of 0.005 per 100 PY represents a background incidence of malignancies in JIA patients reported in a study conducted in Canada. [12]However, a study with sample size of 250 patients in the tofacitinib cohort and 750 patients in the comparator cohort would detect a HR no less than 11.54 for an IR of malignancy of 0.05 per 100 PY, where the IR of 0.05 per 100 PY represents a background incidence of malignancy in JIA patients reported in one study each conducted in Sweden and in the US.[11, 13] Furthermore, a study with sample size of 250 patients in the tofacitinib cohort and 750 patients in the comparator cohort would detect a HR no less than 8.65 and 8.03 for an IR of malignancy of 0.08 and 0.09 per 100 PY, where the IRs of 0.08 and 0.09 per 100 PY represent a background incidence of malignancy in JIA patients in 2 studies conducted in Germany and 1 study conducted in the US.[14,15,16]

In addition to conducting a standardized analysis across the 4 registers (ie, BiKeR, JuMBO, UK JIA Clinical Register and nationwide Swedish healthcare registers), a meta-analysis will be conducted using the study-specific IRs to provide pooled estimates across the 3 PASS using the 4 registers as described in Section 9.7. The anticipated sample size of tofacitinib cohort in the other two studies using nationwide Swedish healthcare registers and the BiKeR/JuMBO registries is 285 and 300 patients, respectively and the anticipated sample of the comparator cohort in the other two studies using nationwide Swedish healthcare registers and the BiKeR/JuMBO registries is 860 and 1,000 patients, respectively. Therefore, a total sample size of the tofacitinib cohort and the comparator cohort is anticipated to be 835 and 2,610 patients across the 3 PASS using the 4 registers, respectively.

The minimum detectable HR comparing tofacitinib-treated patients versus comparator-treated patients are calculated for the different incidence rates and sample sizes (835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort) and presented in Table 3 below. The calculations make the following assumptions: (1) power = 80%, (2) 2-sided $\alpha = 0.05$, (3) 8-year total study duration in this study and the study using the nationwide Swedish healthcare registers (7-years patient uniform accrual, and minimum 1-year follow-up from the last enrolled patient) and 10-year total study duration in the BiKeR/JuMBO study (9-years patient uniform accrual, and minimum 1-year follow-up from the last enrolled patient) and (4) 5% annual loss to follow up or treatment switch for all patients.

Table 4. Minimum Detectable Hazard Ratios Comparing Tofacitinib-Treated Patients versus Comparator-Treated Patients Across the 3 PASS with 80% Power, 2-sided α = 0.05, 10-Year/8-Year Total Study Duration with 9 Years/7 Years of Uniform Accrual, 5% Loss to Follow Up or Treatment Switch Per Year

Assumed IR (per 100 PY) for Comparator Cohort	Sample Size in Tofacitinib Cohort across the 3 PASS	Sample Size in Comparator Cohort across the 3 PASS	Hazard Ratio
0.005†	835	2,610	>14*
0.01†	835	2,610	>14*
0.05†	835	2,610	5.74
0.08†	835	2,610	4.48
0.09†	835	2,610	4.17
0.1§	835	2,610	3.95
0.5§	835	2,610	2.05
1.0¶	835	2,610	1.7

*Infeasible to calculate the exact value due to assumed low IR (expect zero events in both the Tofacitinib cohort and Comparator cohort for the scenarios).
IR=incidence rate; PY=person-year
† The observed IRs of malignancies in the comparator cohort as reported in Horne et al 2019, Bernatsky et al 2011, Nordstrom et al 2012, Barth et al 2017, Beukelman et al 2012, and Horneff et al 2016.
§ The observed IRs of herpes zoster infection in the comparator cohort as reported in Nimmrich et al 2015.
¶ The observed IRs of serious infections in the comparator cohort as reported in Aygun et al 2019.

Based on the information presented in Table 4, the 3 PASS with a total sample size of 835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort would detect a HR no less than 2.05 and 3.95 (tofacitinb versus comparator) for an IR of 0.5 and 0.1 per 100 PY in the comparator cohort, respectively, where the IRs of 0.5 and 0.1 per 100 PY represent a background incidence of herpes zoster infection in JIA patients.[17] Similarly, the 3 PASS with a total sample size of 835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort would detect a HR no less than 1.7 (tofacitinb versus comparator) for an IR of 1.0 per 100 PY in the comparator cohort, where the IR of 1.0 per 100 PY represents a background incidence of serious infections in JIA patients.[18] Lastly, the 3 PASS with a total sample size of 835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort would detect a HR no less than >14 (tofacitinb versus comparator) for an IR of 0.005 per 100 PY in the comparator cohort, where an IR of 0.005 per 100 Py represents a background incidence of malignancy in JIA patients as reported in a study conducted in Canada.[12] However, the 3 PASS with a total sample size of 835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort would detect a HR no less than 5.74 for an IR of malignancy of 0.05 per 100 PY, where the IR of 0.05 per 100 PY represents a background incidence of malignancy in JIA patients reported in one study each conducted in Sweden and in the US. [11, 13]Furthermore, the 3 PASS with a total sample size of 835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort would detect a HR no less than 4.48 and 4.17 for IRs of malignancy of 0.08 and 0.09 per 100 PY, respectively, where the IRs of 0.08 and 0.09 per 100 PY represent a background incidence of malignancy in JIA patients in 2 studies conducted in Germany and 1 study conducted in the US.[14,15,16] Even though the background incidence rates of malignancy in JIA patients range from 0.005 to 0.09 per 100 PY, the incidence rates range from 0.05 to 0.09 per 100 PY in the studies conducted in Sweden and Germany, [11, 14, 16]which may serve as a reasonable background incidence to be applicable to the 3 PASS in Europe. Therefore, it is reasonable to

assume that the minimum detectable HRs will range from 4.17 to 5.74 corresponding to the background IRs of 0.05 to 0.09 per 100 PY.

9.6. Data management

This study is conducted by making secondary use of existing data collected by the UK JIA Biologics Register, which collects data from National Health Services (NHS) trusts under UK Health Research Authority approval and following informed written consent from participants. The University of Manchester has established data management processes in place. For the main analyses and reports for this protocol, the analyses will be undertaken by a statistician employed by The University of Manchester. No raw data will be shared with the Sponsor for the primary analyses. Information on data security at the University of Manchester can be found here: https://sites.manchester.ac.uk/bcrdbspar/for-participants/protecting-your-information/.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. Statistical analyses will be performed using STATA version 13 or higher (www.stata.com). All analyses will be carried out under the direction of the Principal Investigator.

The interim analysis will consist of descriptive comparisons of baseline characteristics of tofacitinib cohort and the comparator cohort. The crude IRs per 100 PYs and 95% CIs of safety events of interest will be estimated in both cohorts. The descriptive analysis will include counts and percentages for categorical data and statistics such as mean, median, standard deviation, and range for continuous variables. The final analysis of endpoints will provide crude IRs of events overall and stratified by baseline characteristics such as disease activity, subtype of JIA, treatment type defined as monotherapy or combination therapy with MTX on the index date, and prior JIA therapy in both tofacitinib cohort and comparator cohort.

In addition to estimating the crude IRs, a comparative analysis will be conducted to examine the risk of the outcomes of interest among patients from the tofacitinib cohort compared to the patients from the comparator cohort adjusting for confounding by baseline characteristics. This comparison will be restricted to the outcomes of interest, where there are adequate data. As the analytic approach to address confounding by risk factors, propensity scores will be estimated using baseline characteristics described in Section 9.3.1 Baseline characteristics. The list of variables to be included in the propensity score estimation will be detailed in the SAP. Propensity score adjusted IR (per 100 PY) and associated 95% CI will be calculated for the outcomes of interest, for which there are adequate data using an exact Poisson method. Additionally, for the outcomes of interest, where there are adequate data to compare the risk between tofacitinib cohort and comparator cohort, multivariable Cox proportional hazards models will be fit to compare risk of the outcome of interest between the tofacitinib cohort and the comparator cohort (details will be included in the SAP). The propensity score will be included in the models based on consideration of balance between treatment groups and potential association with an outcome of interest and HRs and associated 95% CIs will be estimated from the models.

Lastly, to examine the impact of including patients in the comparator cohort from years 2010 to 2029, a sensitivity analysis will be conducted using a subset of the comparator cohort patients recruited during a period from 07 April 2022 to 01 July 2029 aligned with the tofacitinib cohort to reduce any possible time bias and to increase the comparability between the tofacitnib cohort and the comparator cohort.

9.7.1. All outcomes of interest except all malignancies combined (excluding NMSC), NMSC, lymphoma, and lung cancer

All outcomes of interest except all malignancies combined (excluding NMSC), NMSC, lymphoma and lung cancer are thought to potentially occur at a higher rate while on treatment, but that increased risk subsides after the drug is discontinued. These events will be evaluated over a risk window that includes time from drug initiation until 90 days after end of treatment. A 90-day extension risk window minimizes the likelihood that an association between medication exposures and safety events is missed. Also, the 90-day extension 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. As a sensitivity analysis, the analysis of outcomes other than all malignancies combined (excluding NMSC), NMSC, lymphoma and lung cancer will be performed using a 28-day extension risk window.

For patients in the tofacitinib cohort, any safety event that occurs during the 90-day extension risk window following discontinuation of tofacitinib will be attributed to tofacitinib, irrespective of any new medication initiation during the 90-day extension risk window. 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 extension risk window following discontinuation of bDMARD will be attributed to bDMARD, irrespective of any new medication initiation (including tofacitinib) during the 90-day extension risk window.

The provisions for the 90-day extension risk window above will be applied similarly to the 28-day extension risk window.

Explicitly, the risk periods will be defined as follows.

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 (index treatment end date + 90 days, loss to follow-up, death, or study end date).

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).

In addition to using the above risk periods, the outcome of all-cause mortality will be examined using an approach of indefinite risk window as described below in Section 9.7.2. This is because all-cause mortality is not only thought to potentially occur at a higher rate while on treatment, with increased risk subsiding after the drug is discontinued, but it could be delayed relative to the time of

exposure. This approach will be considered a sensitivity analysis. Under this approach, follow-up for each cohort will start on the index date until loss to follow-up, death or end of study.

For the interim analysis, the 'study end date' will be replaced by the data extraction date for the interim report.

For the patients who had an event of interest within a defined risk period, the first event will be used in analyses. For the patients who did not experience the event of interest within the defined risk period or had the event of interest but outside the defined risk period, the patient will be censored to the end of the risk period.

9.7.2. Nonmelanoma skin cancer (NMSC), all malignancies combined excluding NMSC, lymphoma, and lung cancer

NMSC, all malignancies combined excluding NMSC, lymphoma and lung cancer, the manifestation of which is expected to be delayed relative to the time of exposure, the outcomes will be evaluated using two different approaches, an indefinite risk window approach as the primary analysis and a most recent exposure approach as a secondary analysis. In the analyses of all malignancies combined excluding NMSC, NMSC, lymphoma and lung cancer using both approaches, follow-up observation will begin 6 months after the index date (i.e., a 6-month lag time will be used). As a sensitivity analysis, a lag-time of 3 months will also be used for both approaches (i.e, indefinite risk window approach as the primary analysis and a most recent exposure approach as a secondary analysis).

The primary analysis of NMSC, all malignancies combined excluding NMSC, lymphoma and lung cancer will assume an indefinite risk paradigm, as is used in study of malignancy associated with bDMARDs.[19] Under this approach, follow-up for each cohort starts at 6 months after the index date until the first of a malignancy event, loss to follow-up, death or end of study. Follow-up for each exposure cohort continues after switching to a new drug or discontinuation of treatment. This approach maximizes follow-up time and the ability to capture long latency events, ie, events that occur or are detected years after exposure. For patients included in the tofacitinib cohort, any subsequent malignancy event will be attributed to the tofacitinib exposure, irrespective of prior or subsequent use of any other medications, subject to the risk period of interest. For patients included in the bDMARD cohort, any subsequent malignancy event will be attributed to the bDMARD exposure, irrespective of subsequent use of tofacitinib or any other medications. Using this approach, there will be no double counting of events in the indefinite risk of malignancy assessment. Explicitly, the corresponding risk period (named Infinite Risk Period) will be defined as: starting at 6 months after the index date until the earliest of (loss to follow-up, death, or study end date).

For NMSC, all malignancies combined excluding NMSC, lymphoma and lung cancer, secondary analyses that censor follow-up time after a switch to a different treatment class will also be performed (most recent exposure paradigm). Among patients indexed to a bDMARD cohort, follow-up will begin at 6 months after the index date and continue until the first of an event, switch to tofacitinib or non-biologic advanced systemic therapy, loss to follow-up, death, or study end date. Similarly, for tofacitinib, follow-up will begin at 6 months after the index date and continue until the first of an event, switch from tofacitinib to another bDMARD or a non-biologic advanced systemic therapy, loss to follow-up, death or study end date. This approach may not allow sufficient follow-up time to allow for latent effects. However, under an assumption of no latency as in an aggressive

tumor promoter, this approach would detect an increased risk of the safety event of interest among patients initiating tofacitinib compared with patients initiating bDMARDs. This risk period will be named as "Most Recent Exposure Risk Period".

For the 6-month (or 3-months) lag time approach, the events occurred in the first 6-months (or 3-months) from the index date will not be counted. However, 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 the patients who had an event of interest within a defined risk period, the first event will be used in analyses. For the patients who did not experience the event of interest within the defined risk period or had the event of interest but outside the defined risk period, the patient will be censored to the end of the risk period.

For the interim analysis, the 'study end date' will be replaced by the data extraction date for the interim report.

A standardized statistical analysis plan will be used across the 4 registers (ie, BiKeR, JuMBO, UK JIA Clinical Register and nationwide Swedish healthcare registers).

In addition to a standardized analysis across the 4 registers, a meta-analysis will be conducted using the study-specific IRs to provide pooled estimates across the 3 PASS using the 4 registers. The meta-analysis will be conducted using an inverse-variance method. Other approaches of meta-analysis will be explored, if necessary. Further details on the meta-analysis will be described in the SAP. Since the results from A3921407 study using the BiKeR and JuMBO registries with the longest study period will be required for conducting meta-analysis across the 3 PASS using the 4 registers, the meta-analysis results will be submitted to the EMA on 01 May 2033 along with the final study report of A3921407.

9.8. Quality control

This study will be conducted by making secondary use of data collected by the UK JIA Biologics Register, within the Biologic Studies Group (BSG) at the University of Manchester. The JIA Biologics Register team are responsible for data quality control. As part of these established practices, all information received on serious adverse events (SAEs) (ie, date of event and completeness of report) is reviewed for accuracy by clinical staff prior to coding. Reports arise from the hospital team or national registers. For SAEs to be included in analysis, the following information is required, (i) a legible and recognized disorder/signs/symptoms, (ii) event date, and (iii) the name of the drug the patient was on at the time of the event. Where this information is missing, the team contact the hospital to validate and confirm the details around the SAE. The data undergo regular validation checks both manually and automatically.

9.9. Limitations of the research methods

This study is designed to monitor the safety of tofacitinib within the clinical practice setting utilizing the UK JIA Biologics Register. Despite the strengths of the register, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling, endpoint misclassification, and the impact of missing data are of concern in interpreting findings.

First, as a new therapy in the JIA treatment, 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 JIA therapies and physical comorbidities that place patients at risk for events. Biases resulting from channeling may present as increased rates of safety events of interest in the early phases of the study. Comparison to comparators may illuminate such channeling. If feasible, stratification on key indicators of disease severity, patient characteristics and prior JIA therapies may be performed to mitigate the effects of channeling. Trend analyses may be conducted to evaluate rates in tofacitinib patients over time.

Second, the JIA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to patient management. The rates of safety events of interest and their distribution among patient-types may have changed over time. The comparators in this study are not exclusively contemporaneous to tofacitinib treated patients. Therefore, a sensitivity analysis as described in Section 9.7 will be conducted using a subset of comparator cohort patients recruited during a period from 07 April 2022 to 01 July 2029 aligned with the tofacitinib cohort to reduce any possible time bias and to increase the comparability between the tofacitnib and the comparator cohorts. The potential lack of comparable controls and lack of randomization which are known limitations inherent to this type of register make this register vulnerable for confounding. Also, analysis may be unable to identify or control for any changes in rates due to changes in the treatment landscape.

Third, outcome misclassification is a concern within the observational setting due to less stringent monitoring of study outcomes relative to clinical trials. While the UK JIA Clinical Register has an established system to identify and capture endpoint data which requests all events are reported regardless of any presume relationship with the child's medication, all events cannot be fully verified via source documentation.

Fourth, this study will follow patients for a period of up to 8 years from initiation of tofacitinib and approved bDMARDs. Conclusions may not be generalizable outside of the 8-year period since initiation of therapy. Also, certain outcomes of interest such as malignancies and growth or development disturbances may occur after a long latency period longer than 8 years, in which case the 8-year follow-up may not be adequate to examine the incidence of such outcomes. Furthermore, if the incidence rate of malignancy is found to be low (i.e, 0.01 or 0.005 per 100 PY), this study and the meta-analysis conducted using the study-specific IRs to provide pooled estimates across the 3 PASS using the 4 registers may not be sufficiently powered to detect a meaningful difference in the risk of malignancy between the tofacitinib and the comparator cohort.

Fifth, missing data in observational research is commonplace. Whilst every effort is made to capture data on all variables, for reasons beyond the control of the registry team, some data may not be captured or recorded in the medical record.

Sixth, information on Tanner stage assessment is not available in the UK JIA Biologics Register; hence, assessment of the outcome of growth and development disturbances will not include Tanner stage assessment.

Lastly, conclusions from this study may be limited to the UK JIA population. Generalizability to other populations, particularly those with different modes of healthcare delivery, may be limited

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves 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 from patients by Pfizer is not required. However, informed consents are obtained from patients at the time of enrollment into the UK JIA Biologic Register.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

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

One interim study report will be generated. Analysis using linked register data through 8-years of follow up will be the basis for a final study report. The interim and final study reports will be submitted to regulatory authorities. The final study report will be posted on EU PAS register. Data may be used in regulatory communications external to UK for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for publication purposes and EMA will be notified upon acceptance for publication.

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 party responsible for collecting data from the participant 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.

13. REFERENCES

1. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.

2. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet 2011;377:2138-49.

3. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014 Mar;81(2):112-7.

4. Davies R, De Cock D, Kearsley-Fleet L, Southwood T, Baildam E, Beresford MW, Foster HE, Thomson W, Ramanan AV, Hyrich KL; British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN) and the Biologics for Children with Rheumatic Diseases (BCRD) study. The risk of uveitis in patients with JIA receiving etanercept: the challenges of analysing real-world data. Rheumatology (Oxford). 2020 Jun 1;59(6):1391-1397.

5. Kearsley-Fleet L, Heaf E, Davies R, Baildam E, Beresford MW, Foster HE, Southwood TR, Thomson W, Hyrich KL; BCRD and BSPAR-ETN study groups. Frequency of biologic switching and the outcomes of switching in children and young people with juvenile idiopathic arthritis: a national cohort study. Lancet Rheumatol. 2020 Mar 9;2(4):e217-e226.

6. Kearsley-Fleet L, Vicente González L, Steinke D, Davies R, De Cock D, Baildam E, Beresford MW, Foster HE, Southwood TR, Thomson W, Hyrich KL; Biologics for Children with Rheumatic Diseases (BCRD) Study and the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN). Methotrexate persistence and adverse drug reactions in patients with juvenile idiopathic arthritis. Rheumatology (Oxford). 2019 Mar 8;58(8):1453–8.

7. Kearsley-Fleet L, Sampath S, McCann LJ, Baildam E, Beresford MW, Davies R, De Cock D, Foster HE, Southwood TR, Thomson W, Hyrich KL. Use and effectiveness of rituximab in children and young people with juvenile idiopathic arthritis in a cohort study in the United Kingdom. Rheumatology (Oxford). 2019 Feb 1;58(2):331-335.

8. Grigoletto V, Occhipinti AA, Pellegrin MC, Sirchia F, Barbi E, Tornese G. Definition and prevalence of familial short stature. Ital J Pediatr. 2021 Mar 9;47(1):56. doi: 10.1186/s13052-021-01018-3. PMID: 33750447; PMCID: PMC7941953.

9. Pedicelli S, Peschiaroli E, Violi E, Cianfarani S. Controversies in the definition and treatment of idiopathic short stature (ISS). J Clin Res Pediatr Endocrinol. 2009;1(3):105-15. doi: 10.4008/jcrpe.v1i3.53. Epub 2009 Feb 1. PMID: 21274395; PMCID: PMC3005647.

10. McErlane F, Carrasco R, Kearsley-Fleet L, Baildam EM, Wedderburn LR, Foster HE, Ioannou Y, Chieng SEA, Davidson JE, Thomson W, Hyrich KL. Growth patterns in early juvenile idiopathic arthritis: Results from the Childhood Arthritis Prospective Study (CAPS). Semin Arthritis Rheum. 2018 Aug;48(1):53-60.

11. Horne A, Delcoigne B, Palmblad K, et al. Juvenile idiopathic arthritis and risk of cancer before and after the introduction of biological therapies. RMD Open 2019;5:e001055.

12. Bernatsky S, Rosenberg AM, Oen KG, Duffy CM, Ramsey-Goldman R, Labrecque J, St Pierre Y, Clarke AE. Malignancies in juvenile idiopathic arthritis: a preliminary report. J Rheumatol. 2011 Apr;38(4):760-3.

13. Nordstrom BL, Mines D, Gu Y, Mercaldi C, Aquino P, Harrison MJ. Risk of malignancy in children with juvenile idiopathic arthritis not treated with biologic agents. Arthritis Care Res (Hoboken). 2012 Sep;64(9):1357-64.

14. Barth S, Schlichtiger J, Hartmann B, Bisdorff B, Michels H, Radon K, Hügle B, Walsh L, Haas JP. Incidence of malignancies in patients with juvenile idiopathic arthritis: A retrospective single-center cohort study in Germany. Mod Rheumatol. 2017 Jan;27(1):60-65.

15. Beukelman T, Haynes K, Curtis JR, Xie F, Chen L, Bemrich-Stolz CJ, Delzell E, Saag KG, Solomon DH, Lewis JD; Safety Assessment of Biological Therapeutics Collaboration. Rates of malignancy associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012 Apr;64(4):1263-71.

16. Horneff G, Klein A, Oommen PT, Hospach A, Foeldvari I, Feddersen I, Minden K. Update on malignancies in children with juvenile idiopathic arthritis in the German BIKER Registry. Clin Exp Rheumatol. 2016 Nov-Dec;34(6):1113-1120.

17. Nimmrich S, Horneff G. Incidence of herpes zoster infections in juvenile idiopathic arthritis patients. Rheumatol Int. 2015 Mar;35(3):465-70. doi: 10.1007/s00296-014-3197-6.

18. Aygun D, Sahin S, Adrovic A, Barut K, Cokugras H, Camcıoglu Y, Kasapcopur O. The frequency of infections in patients with juvenile idiopathic arthritis on biologic agents: 1-year prospective study. Clin Rheumatol. 2019 Apr;38(4):1025-1030.

19. Haynes K, Beukelman T, Curtis JR, Newcomb C, Herrinton LJ, Graham DJ, Solomon DH, Griffin MR, Chen L, Liu L, Saag KG, Lewis JD; SABER Collaboration. Tumor necrosis factor α inhibitor therapy and cancer risk in chronic immune-mediated diseases. Arthritis Rheum. 2013 Jan;65(1):48-58.

14. LIST OF TABLES

Table 1. Information on vaccinations captured in the UK JIA Biologics Register

Table 2. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and person-years

Table 3. Table 3. Minimum Detectable Hazard Ratios Comparing Tofacitinib-Treated Patients versus Comparator-Treated Patients with 80% Power, 2-sided α = 0.05, 8-Year Total Study Duration with 7 Years of Uniform Accrual, 5% Loss to Follow Up or Treatment Switch Per Year

Table 4. Minimum Detectable Hazard Ratios Comparing Tofacitinib-Treated Patients versus Comparator-Treated Patients Across the 3 PASS with 80% Power, 2-sided α = 0.05, 10-Year/8-Year Total Study Duration with 9 Years/7 Years of Uniform Accrual, 5% Loss to Follow Up or Treatment Switch Per Year

15. LIST OF FIGURES

Figure 1. Follow-up times for patients based on the date of initiation of tofacitinib

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

1. MedDRA codes used for identification of outcomes of interest

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
Venous thromboembolism	SMQ Narrow | Embolic and thrombotic events, venous
Serious infections and other important infections (such as opportunistic infection, tuberculosis and vaccine preventable infections)	*(Adverse events that met serious criteria only)* SOC | Infections and infestations [Primary path] PT | Febrile neutropenia *For Tuberculosis only*: HLT | Mycobacteria identification and serology [Primary path] HLT | Tuberculous infections [Primary path] *Use in Asians* Race = Asian *AND/OR* Country where event occurred = China; Hong Kong; India; Japan; Korea, Republic Of (South Korea); Malaysia; Philippines; Singapore; Taiwan, Province Of China; Thailand; Vietnam *For Coronavirus infection only:*

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	(Search for cases that report any of the following PTs (as PT Event *OR* PT Patient Medical History *OR* PT Indication): PT | Asymptomatic COVID-19 PT | Coronavirus infection PT | Coronavirus test positive PT | Coronavirus test PT | COVID-19 pneumonia PT | COVID-19 prophylaxis PT | COVID-19 treatment PT | COVID-19 PT | Exposure to SARS-CoV-2 PT | Occupational exposure to SARS-CoV-2 PT | SARS-CoV-2 antibody test PT | SARS-CoV-2 antibody test positive PT | SARS-CoV-2 carrier PT | SARS-CoV-2 sepsis PT | SARS-CoV-2 test false negative PT | SARS-CoV-2 test positive PT | SARS-CoV-2 test PT | SARS-CoV-2 viraemia PT | Suspected COVID-19 PT | Congenital COVID-19 PT | Post-acute COVID-19 syndrome PT | SARS-CoV-2 RNA PT | SARS-CoV-2 RNA decreased PT | SARS-CoV-2 RNA fluctuation PT | SARS-CoV-2 RNA increased PT | Vaccine derived SARS-CoV-2 infection
All malignancies combined (excluding NMSC)	SMQ Narrow | Malignancy related conditions SMQ Narrow | Malignancy related therapeutic and diagnostic procedures SMQ Narrow | Malignant or unspecified tumours SMQ Narrow | Tumour markers *See NMSC for NMSC-specific code exclusion*
Lymphoma (examined as a separate outcome)	SMQ Narrow | Malignant lymphomas
Lung cancer (examined as a separate outcome)	HLT | Respiratory tract and pleural neoplasms malignant cell type unspecified NEC (Primary Path) • Exclude PT Throat cancer

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	HLT | Lower respiratory tract neoplasms (Primary Path) • Exclude PTs: Benign lung neoplasm, Benign respiratory tract neoplasm, Bronchial neoplasm benign, Endobronchial lipoma, Sclerosing pneumocytoma HLT | Non-small cell neoplasms malignant of the respiratory tract cell type specified (Primary Path) PT | Carcinoid tumour pulmonary PT | Metastases to lung LLT | Kaposi's sarcoma, lung
Gastrointestinal perforations	SMQ Narrow | Gastrointestinal perforation PT | Abscess bacterial PT | Abscess rupture PT | Appendicectomy PT | Appendicitis PT | Biliary abscess PT | Colitis PT | Diverticulitis PT | Diverticulum PT | Gallbladder abscess PT | Liver abscess PT | Pancreatic abscess PT | Pelvic abscess PT | Perihepatic abscess PT | Postoperative abscess PT | Pyloric abscess PT | Rectovaginal septum abscess PT | Splenic abscess PT | Subdiaphragmatic abscess
Major adverse cardiac events (including MI)	SMQ Narrow | Central nervous system vascular disorders SMQ Narrow | Myocardial infarction SMQ Narrow | Other ischaemic heart disease PT | Cardiac death PT | Cardiac failure congestive PT | Sudden cardiac death PT | Pulmonary embolism
Hypersensitivity	HLGT | Allergic conditions HLT | Allergic conditions NEC

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	HLT | Allergies to foods, food additives, drugs and other chemicals HLT | Anaphylactic and anaphylactoid responses HLT | Angioedemas HLT | Atopic disorders HLT | Urticarias
Growth or development disturbances	Will be assessed using height velocity z-scores, and BMI z-scores. See Section 9.3.4 Outcomes of Interest for specifics.
Fractures	HLGT | Bone and joint injuries (Primary Path) • Exclude all PTs within HLT Bone and joint injuries NEC • Exclude the following individual PTs from other HLTs: Bone fissure, Cuboid syndrome, Fracture delayed union, Fracture infection, Fracture nonunion, Joint dislocation, Joint dislocation pathological, Metaphyseal corner fracture, Pathological fracture, Pseudarthrosis, Pseudofracture, Anterior labroligamentous periosteal sleeve avulsion lesion, Bankart lesion, Fracture of clavicle due to birth trauma, Radial head dislocation, Scapulothoracic dissociation, Dislocation of vertebra, Intervertebral disc injury, Spinal fusion fracture, Costal cartilage fracture, Costochondral separation, Dislocation of sternum. HLGT | Fractures (Primary Path) • Exclude all PTs within HLT Fracture complications
Progressive multifocal leukoencephalopathy (PML)	PT | JC polyomavirus test positive PT | JC virus infection PT | Leukoencephalopathy PT | Progressive multifocal leukoencephalopathy
Herpes zoster (HZ) reactivation	PT | Disseminated varicella zoster virus infection PT | Genital herpes zoster PT | Herpes zoster PT | Herpes zoster cutaneous disseminated PT | Herpes zoster disseminated PT | Herpes zoster infection neurological PT | Herpes zoster meningitis PT | Herpes zoster meningoencephalitis PT | Herpes zoster meningomyelitis PT | Herpes zoster meningoradiculitis PT | Herpes zoster necrotising retinopathy PT | Herpes zoster oticus

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	PT | Herpes zoster pharyngitis PT | Herpes zoster reactivation PT | Ophthalmic herpes zoster *Use in Asians* Race = Asian *AND/OR* Country where event occurred = China; Hong Kong; India; Japan; Korea, Republic Of (South Korea); Malaysia; Philippines; Singapore; Taiwan, Province Of China; Thailand; Viet Nam
Non-melanoma Skin Cancer (NMSC)	HLT | Skin neoplasms malignant and unspecified (excl melanoma) (Primary path) PT | Squamous cell carcinoma
Interstitial lung disease	SMQ Broad and Narrow | Interstitial lung disease *Use in Asians* Race = Asian *AND/OR* Country where event occurred = China; Hong Kong; India; Japan; Korea, Republic Of (South Korea); Malaysia; Philippines; Singapore; Taiwan, Province Of China; Thailand; Viet Nam
All-cause mortality	Clinical outcome = Fatal
Footnote: The most recent MedDRA version available at the time of analysis will be used for interim and final report analysis.	

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile Psoriatic Arthritis within the UK JIA Biologics Register

EU PAS Register® number:
Study reference number (if applicable): A3921409

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	Abstract
1.1.3 Progress report(s)	☐	☐	☒	milestones
1.1.4 Interim report(s)	☒	☐	☐	and Section 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Milestones
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1 and 9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	11

Comments:

Comparative analysis is added in Section 9.7.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	9.1, 9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.1, 9.2.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.5 Duration of follow-up	☒	☐	☐	9.3.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1.2

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

List of MedDRA codes is added in Annex 1 of the protocol.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Comparative analysis as described in Section 9.7 addresses confounding.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2, 9.3.2, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2, 9.3.4, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2, 9.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6

Comments:

MedDRA codes are included in Annex 1 of the protocol.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7, 9.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	Acknowledged as a limitation in 9.9
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	Acknowledged as a limitation in 9.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3, 10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Sampada Gandhi

Date: 07/July/2022

Signature: Sampada Gandhi

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921409_TOFA JIA PASS UK JIA REGISTER PROTOCOL_V1.0_ 03MAY2023
Document Title:	A3921409_TOFA JIA PASS UK JIA REGISTER PROTOCOL_V1.0_ 03MAY2023

Signed By:	Date(GMT)	Signing Capacity
De Bernardi, Barbara	11-May-2023 21:03:46	EUQPPV Approval
Younus, Muhammad	12-May-2023 12:21:28	Final Approval