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 German Biologics in Pediatric Rheumatology Registry (BiKeR) and Juvenile Arthritis Methotrexate/Biologics Long-term Observation (JuMBO) Registries
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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 German Biologics in Pediatric Rheumatology Registry (BiKeR) and Juvenile Arthritis Methotrexate/Biologics long-

	term Observation (JuMBO) Registries 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	Germany
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College for Rheumatology
AE	adverse event
ATC	Anatomical Therapeutic Chemical
bDMARDs	biological disease-modifying antirheumatic drugs
BID	twice daily
BiKeR	German Biologics in Pediatric Rheumatology Registry
BMI	body mass index
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
cJADAS10	clinical Juvenile Arthritis Disease Activity Score 10
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
DRFZ	Deutsches Rheuma-Forschungszentrum Berlin
EMA	European Medicines Agency
ENCePP	The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERA	enthesitis-related arthritis
ESI	events of special interest
ESR	erythrocyte sedimentation rate

EU	European Union
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GI	gastrointestinal
GKJR	Gesellschaft für Kinder- und Jugendrheumatologie
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HAQ	Health Assessment Questionnaire
HR	hazard ratio
HLA	human leukocyte antigen
HRQoL	health-related quality of life
HZ	Herpes Zoster
IC	informed consent
ICD	International Classification of Diseases
ID	identification
IEC	Independent Ethics Committee
ILAR	International League of Associations for Rheumatology
IR	incidence rate
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IT	information technology
JAK	Janus Kinase
JADAS	Juvenile Arthritis Disease Activity Score

JIA	juvenile idiopathic arthritis
JuMBO	Juvenile Arthritis Methotrexate/Biologics Long-term Observation
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTX	methotrexate
NI	non-interventional
NMSC	nonmelanoma skin cancer
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NNH	numbers needed to harm
PASS	Post-authorization safety study
pedACR	Paediatric American Colleague of Rheumatology
pcJIA	polyarticular-course juvenile idiopathic arthritis
PI	principal investigator
pJIA	polyarticular juvenile idiopathic arthritis
PML	Progressive multifocal leukoencephalopathy
PsA	psoriatic arthritis
PY	person-year
QALY	quality-adjusted life year
RA	rheumatoid arthritis
RCC	Register-Coordinating Center
RF	rheumatoid factor

RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SARS-Cov-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SDS	standard deviations scores
sJIA	systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
SPSS	Statistical Package for the Social Sciences
UC	ulcerative colitis
UK	United Kingdom
VAS	visual analogue scale
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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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 German Biologics in Pediatric Rheumatology Registry (BiKeR) and Juvenile Arthritis Methotrexate/Biologics Long-term Observation (JuMBO) Registries

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  Date: 03 May 2023

  Author: Sampada Gandhi, Pfizer, Inc.

- Rationale and background: Juvenile idiopathic arthritis (JIA) is a heterogenous group of conditions, defined as arthritis persisting for 6 weeks or longer with no other identifiable cause and onset prior to age 16. 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, fractures, malignancy [excluding NMSC] and NMSC, lymphoma, lung cancer, interstitial lung disease, 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 BiKeR and JuMBO registries from Germany 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 BiKeR and JuMBO registries 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 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 patients with pJIA or juvenile PsA from the two German registries separately, namely the BiKeR and JuMBO registries.

- Population: The study population will comprise all patients with pJIA or juvenile PsA enrolled within the BiKeR and JuMBO registries who receive tofacitinib following product availability in Germany on 01 March 2022 through 01 July 2031. One comparator cohort comprised of patients with pJIA or juvenile PsA treated with approved bDMARDs 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, subtype of JIA, comorbidities, 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: BiKeR is a longitudinal, multicenter observational registry from Germany that has been prospectively collecting data from JIA patients treated with biologic therapies in standard clinical practice for approximately twenty years (established in year 2001). The registry was established by pediatric rheumatologists to prospectively monitor the long term safety and effectiveness of biologic treatments. The registry captures a network of approximately 80 sites with pediatric rheumatologists and since inception has followed approximately 5000 patients. JuMBO was launched in 2007 in Germany as the BiKeR follow-up registry with the aim of assessing the long-term safety and effectiveness of disease-modifying antirheumatic drugs (DMARDs) in adult patients with JIA under real-life conditions. All patients followed in JuMBO were previously enrolled in BiKeR and are being or had been treated with a biologic and/or conventional synthetic DMARD (csDMARDs). After enrollment in BiKeR, the planned follow-up period is a minimum of 15 years, including at least 5 years in JuMBO. So far, more than 400 rheumatology sites have participated in JuMBO and enrolled approximately 1850 patients. Approximately 130 patients are transferred from BiKeR to JuMBO each year.

- Study size: This is a descriptive study without pre-specified hypotheses. All eligible patients enrolled in the two registries following product availability in Germany on 01 March 2022 through 01 July 2031 will be included in both cohorts, with no upper limit on the sample size. Approximately 300 and 1000 patients are expected to be identified from the BiKeR registry in the tofacitinib cohort and bDMARD comparator cohort, respectively.

- Data analysis: Descriptive analyses will be performed to summarize baseline demographic and clinical characteristics of the tofacitinib and comparison cohorts. Crude IRs per 100 person-years (PY) and 95% confidence intervals (CIs) of outcomes 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 2032

Final study report: 01 May 2033

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Registration in the European Union (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 2032
Final study report	01 May 2033

* 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 International League of Associations for Rheumatology (ILAR) has classified JIA into 7 distinguishable subtypes as follows: rheumatoid factor (RF)+ polyarthritis, RF- polyarthritis, oligoarthritis (persistent and extended), systemic JIA (sJIA), juvenile psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis.[1] JIA is the most common pediatric rheumatic illness, with an annual incidence in developed countries of 2 to 20 per 100,000 children and a prevalence of 16 to 150 per 100,000.[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 EU in August 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), HZ, malignancy (excluding NMSC) and NMSC, lymphoma, lung cancer, 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. Furthermore, 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 IRs 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, nationwide Swedish healthcare registers, and the United Kingdom (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 BiKeR and JuMBO registries. 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 IRs of safety events of special interest in patients with pJIA or juvenile PsA in the BiKeR and JuMBO registries 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 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 10-year active surveillance, secondary data collection study of patients with pJIA or juvenile PsA using data from the BiKeR and JuMBO registries from Germany from the years 2022 to 2032.

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 01 March 2022 (corresponding to Tofacitinib availability in Germany) to 01 July 2032.

BiKeR Registry

The German BiKeR registry is a longitudinal multicenter observational registry that is an initiative of the Centre for Pediatric Rheumatology Sankt Augustin supported by the German Society for Childhood Rheumatology [Gesellschaft für Kinder- und Jugendrheumatologie (GKJR)]. The registry was set up in 2001 by pediatric rheumatologists in Germany to prospectively monitor the long term safety and effectiveness of biologics in treatment of JIA.[4] All participating physicians are board-certified pediatric rheumatologists. The BiKeR registry includes about 80 study sites and since its inception has followed approximately 5000 patients in Germany. The BiKeR registry includes pediatric patients, aged 2 to 18 years, who meet ILAR criteria for JIA[1] when they initiate biologic therapy or methotrexate (MTX). However, the registry excludes patients who are pregnant at the time of registry entry or, for regulatory reasons, receive biologic therapy which are not approved for JIA patients (off label). The BiKeR patient population is generally comparable to other MTX- and biologic-eligible JIA populations in EU countries in terms of age of onset, age of treatment initiation, gender, JIA subcategory distribution, history of uveitis, human leukocyte antigen (HLA) B27 positivity, pretreatment and co-treatment with steroids and MTX.[0, 6, 7, 8] It thus appears that the BiKeR population is representative of the EU JIA population. Over time, newly approved biologics have been added as exposures of interest. Data from the BiKeR registry have been used to perform post-marketing safety studies for etanercept, adalimumab and other biologics.[9,10]

Patient demographic characteristics, disease history, and previous treatments are documented at the time of patient enrollment. Details about relevant treatment and reasons for discontinuation, concomitant therapy, disease activity and data on safety events of interest are prospectively collected using standard case report forms (CRFs) from the start of treatment and during follow-up.[4] These follow-up intervals represent intervals from routine clinical care and are sufficient to monitor the effects of the drugs, even if the response is not immediate. Patients are followed from enrollment in the registry until they transfer out of pediatric rheumatology practices upon reaching adulthood around their 18th birthday.

Over time, BiKeR CRFs have been updated to reflect concerns about new potential risks for biologic agents. The current registry CRF includes a list of safety events of interest. This list will be expanded to include additional safety events of interest specific to this PASS (such as thromboembolic events) to systematically collect information on these events. The updated CRF will be used across the BiKeR registry at each visit moving forward. In addition to these pre-specified safety events of interest, treating physicians are able to report other safety events of interest that may arise during follow-up.

JuMBO Registry

As described above, the national JIA biologics register BiKeR was set up in 2001 to assess the safety and effectiveness of bDMARDs under real-life conditions, a few months after the approval of the first biologic drug, i.e., etanercept, for JIA in Germany.[4] During the first six years of BiKeR, one-third of patients were lost to follow-up for age-related reasons. It is recognized that follow-up of patients beyond adolescence is necessary to yield scientifically rigorous long-term safety information about bDMARDs in JIA patients. Therefore, JuMBO was launched as the BiKeR follow-up register for adult JIA patients in 2007.

Since 2007, approximately 250 patients with JIA reach adulthood in BiKeR per year and of these, JuMBO has recruited approximately 130 young adults per year. These patients are followed into

adulthood. The register has found nationwide acceptance, which is reflected in the number of participating rheumatology sites, which exceeds 400 with approximately 1850 patients enrolled. So far, close patient monitoring has resulted in a relatively low dropout rate of 15% after the first JuMBO visit. All patients followed in JuMBO were formerly included in BiKeR and are being or were previously treated with a bDMARD and csDMARD. Each subject is followed prospectively for at least 15 years after enrollment in BiKeR and start with a specific bDMARD or MTX, and for at least 5 years in JuMBO. BiKeR registry retains patients by monitoring patient visits and via email reminders at large centers where 80% of the patients are enrolled to minimise loss to follow-up.

Patients are half-yearly assessed in both ways, by a physician and via a patient questionnaire. The data collected includes safety, effectiveness, and treatment adherence information for JIA patients exposed to any biologic and/or non-biologic agent. The type of treatment administered and the conduct of individual therapy, including dosages, are determined by the treating physician only. Patients discontinuing drugs remain included in the register cohort, regardless of their new treatment. Safety events of interest occurring during the observation period are recorded by physicians, regardless of the patient's current treatment. Protocol-defined events of special interest (ESI) are recorded via specific report forms. In addition to physician-reported safety events of interest, patients are asked to report health problems. Confirmation of every potentially serious patient-reported event is sought from each physician involved in the care of the particular patient. Therefore, JuMBO enables the identification of important safety events of interest and their associations with therapeutic agents. As most bDMARDs have been licensed for the treatment of polyarticular-course juvenile idiopathic arthritis (pcJIA), most safety data refer to patients with pcJIA, who account for more than half of the patients included in JuMBO.

In addition to answering questions about the safety of DMARDs, the data collected in JuMBO allow for analysis of treatment patterns in JIA in adulthood, long-term clinical and patient-centered outcomes, and the cost of the illness.

In general, BiKeR and JuMBO registries have been used in previously published studies to assess the safety and effectiveness of DMARDs in JIA patients [9,11,12] and these registries aim to provide results that help to guide therapeutic decisions by providers for affected children, families; to improve post-marketing drug surveillance; and to reduce cost.

9.2.1. Inclusion criteria

The active surveillance population includes patients with pJIA or juvenile PsA enrolled in the BiKeR and JuMBO registries who are newly treated with tofacitinib (tofacitinib cohort) following EU approval (August 2021) and launch of the product in Germany (product is available in Germany since 01 March 2022). For contextualization purposes, the study population will also include a comparator cohort as defined in inclusion/exclusion criteria. Patients are eligible to move between cohorts if inclusion/exclusion criteria are met.

9.2.1.1. BiKeR registry

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the BiKeR tofacitinib and comparator cohorts:

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

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

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 01 March 2022 through 01 July 2031 and as captured in the BiKeR registry

9.2.1.1.2. 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 Germany (e.g., etanercept, adalimumab, abatacept, tocilizumab, golimumab). 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 March 2022 to 01 July 2031 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 identified from the BiKeR registry between 01 March 2022 through 01 July 2031

9.2.1.2. JuMBO registry

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the JuMBO tofacitinib and comparator cohorts:

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

1. Must be previously enrolled in BiKeR registry

2. Diagnosis of pJIA defined as extended oligoarthritis, polyarthritis (RF+), or polyarthritis (RF-) or a diagnosis of juvenile PsA by a pediatric or adult rheumatologist

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

4. Patients aged 2-17 years at tofacitinib initiation

5. Initiation of tofacitinib as a monotherapy or in combination with MTX following product availability on 01 March 2022 through 01 July 2031 and as captured in the JuMBO registry

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

1. Must be previously enrolled in BiKeR registry

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

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

4. Patients aged 2-17 years at initiation of any bDMARD approved for pJIA or juvenile PsA treatment in Germany (e.g., etanercept, adalimumab, abatacept, tocilizumab, golimumab). 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 March 2022 to 01 July 2031 will be eligible regardless of this patient's prior use of another bDMARD, for example tocilizumab.

5. Patients initiating a bDMARD as a monotherapy or in combination with MTX identified from the JuMBO registry between 01 March 2022 through 01 July 2031

9.2.2. Exclusion criteria

The same exclusion criteria as listed below will be applied to both the BiKeR and JuMBO registries. 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 prior to the start of the index therapy (tofacitinib or bDMARDs), ie., index date. Index date will be defined as the date of start of first treatment for tofacitinib and bDMARDs in the tofacitinib and the comparator cohort, respectively.

9.3.1.1. Demographic characteristics

9.3.1.1.1. BiKeR registry

Information on the following variables will be extracted from the BiKeR registry database prior to the index date: age at cohort entry, sex (male, female, diverse gender), race/ethnicity, and geographic region (only residents from Germany will be included). Age at cohort entry will be defined as age on

the index date. It will be calculated as index date minus date of birth (or month and year of birth). At inclusion, patients must be older than 2 years and younger than 18 years.

9.3.1.1.2. JuMBO registry

Information on the following variables will be extracted from the BiKeR registry database prior to the index date: age at cohort entry, sex (male, female, diverse gender and as extracted from BiKeR), race/ethnicity (as extracted from BikeR), and geographic region (identified for each patient by postal code and country code). Months and year of birth will be extracted from the BiKeR registry. Month and year of birth will also be collected in JuMBO in order to correctly match the patient in the BiKeR registry for transfer to JuMBO. Age will be defined as age at JuMBO enrollment. It will be calculated as date of enrollment in JuMBO minus date of birth. Sex is also be collected in JuMBO in order to correctly match the patient in the BiKeR registry for transfer to JuMBO.

9.3.1.2. Calendar year of cohort entry

9.3.1.2.1. BiKeR registry

Enrollment of patients will start from 01 March 2022 and end on 01 July 2031.

9.3.1.2.2. JuMBO registry

Enrollment of patients will start as soon as the first study patient is transferred from BiKeR during the study period from 01 March 2022 to 01 July 2031.

9.3.1.3. Disease activity

Disease activity will be assessed using the pediatric ACR (pedACR) core criteria and Juvenile Arthritis Disease Activity Score (JADAS) in both registries as described below.

9.3.1.3.1. Pediatric ACR score

Disease activity will be assessed using the pedACR core criteria. For this, the following items will be assessed prior to the index date.

- Physician’s global assessment of disease activity [visual analogue scale (VAS)]
- Parents' global assessment of subject's overall well-being Parent/patient’s global assessment of disease Activity (VAS)
- CHAQ (Childhood Health Assessment Questionnaire), German version in BiKeR registry and HAQ (Health Assessment Questionnaire), German version in JuMBO registry
- Number of joints with active arthritis defined as swollen and/or tender joints with limited range of motion
- Number of joints with limited range of motion
- Erythrocyte sedimentation rate (ESR) as available or C-reactive protein (CRP) as available

9.3.1.3.2. Juvenile Arthritis Disease Activity Score (JADAS)

The JADAS10 and the JADAS71 will be calculated prior to the index date. For this the following items will be assessed:

- Physician's global assessment of disease activity [visual analogue scale (VAS)]
- Parent/patient's global assessment of disease Activity (VAS)
- Number of joints with active arthritis defined as swollen and/or tender joints with limited range of motion
- ESR as available
- CRP as available

In addition, the clinical JADAS10 (cJADAS 10) will be calculated based on the physician's global assessment of disease activity (VAS) [(Numeric rating scale or NRS 0-10)], parent/patient's global assessment of disease Activity (NRS 0-10), and number of joints with active arthritis defined as swollen and/or tender joints with limited range of motion.

9.3.1.4. JIA subtype [based on ILAR classification[1]]

- Polyarthritis RF-: defined as arthritis affecting more than four joints during the first 6 months of disease; test results for RF are negative
- Polyarthritis RF+: defined as arthritis affecting more than four joints during the first 6 months of disease; test results for RF are positive (on at least two occasions more than 3 months apart)
- Oligoarthritis extended: defined as arthritis affecting a total of more than four joints after the first 6 months of disease
- Juvenile PsA: defined as arthritis and psoriasis or arthritis and at least two of the following:
  - Dactylitis
  - Nail abnormalities (pitting or onycholysis)
  - Psoriasis in a first-degree relative

Patients fulfilling the criteria for other JIA subtypes or for no or more than 1 JIA subtype will be excluded.

9.3.1.5. Duration of JIA

Duration of JIA will be calculated as the index date minus the date of diagnosis extracted from BiKeR in both registries.

9.3.1.6. Age at JIA diagnosis

Age at diagnosis is available in the BiKeR registry given for the first time independent from the start of symptoms. This information will be used for both registries as the date of JIA diagnosis is not available in JuMBO.

9.3.1.7. Prior JIA therapy

The following JIA therapies received prior to the index date will be of interest: systemic glucocorticoids such as prednisone, prednisolone, methylprednisolone, nonsteroidal anti-inflammatory drugs (NSAIDs), csDMARDs such as (but not limited to) MTX, sulfasalacine, leflunomide, cyclosporine A, azathioprine, mycophenolic mofetil, and bDMARDs such as (but not limited to) etanercept, adalimumab, golimumab. certolizumab, infliximab, abatacept, tocilizumab, sarilumab, ixekizumab, secukinumab. The prior use of all DMARDs will be recorded at JuMBO enrollment. In addition, treatment data will be extracted from BiKeR in order to get the complete treatment history.

9.3.1.8. Comorbidities

The history of comorbidities including infections and autoimmune diseases, uveitis, allergies and psoriasis will be recorded in both registries at baseline. Comorbidities and adverse events (AE) are coded according to MedDRA coding system and each AE receives a primary term code.

9.3.1.9. Concomitant medications

In both registries, all pharmacomedical treatment will be recorded independently from the relationship to the JIA diagnosis. Data on concomitant medications such as MTX, systemic glucocorticoids such as prednisone, prednisolone, methylprednisolone and NSAIDs, and key non-JIA therapies (e.g., therapies used in the treatment of comorbidities) will be recorded.

9.3.1.10. Body mass idex (BMI)

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

9.3.1.11. Vaccination status at baseline and during follow-up

9.3.1.11.1. BiKeR registry

The vaccination status is recorded at BiKeR enrollment. Recommended vaccinations in childhood and adolescence in Germany such as varicella, polio or meningococcal vaccine as well as SARS-CoV-2 are recorded. At each visit, patients indicate all vaccinations received within the last 6 months.

9.3.1.11.2. JuMBO registry

The history of vaccinations is extracted from BiKeR. At each visit, patients indicate all vaccinations received within the last 6 months.

9.3.2. Exposure ascertainment

Exposure to tofacitinib, approved bDMARDs and MTX will be identified from the BiKeR registry using the name of active substance and via Anatomical Therapeutic Chemical (ATC) drug codes from the JuMBO registry. Duration of exposure to tofacitinib and approved bDMARDs will be calculated from the start and end date of each respective exposure treatment in both registries. In addition, dose and frequency of exposure treatments of tofacitinib and approved bDMARDs will be described in both registries.

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

Patients will be followed from the index date until the first occurrence of each outcome of interest, death, or end of study period (ie, 01 July 2032) 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 reports. All outcomes, with the exception of growth or development disturbances, will be identified using the Medical Dictionary for Regulatory Activities (MedDRA) codes in both registries. 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, BMI z-scores, and Tanner stage assessments, to evaluate growth disturbances, weight disturbances, and pubertal development, 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. As 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 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.[13, 14,15] 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 captured at baseline, BMI z-scores will be calculated based on measurements obtained at each follow-up visit.

  - Tanner stage assessment[16, 17]: Tanner stage assessment is available in the BiKeR registry as a measure of pubertal development, whereas it is not applicable to the adult patients with pJIA and PsA identified from the JuMBO registry; hence, Tanner stage assessment will not be included for patients identified from the JuMBO registry.

- 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 BiKeR and JuMBO registries 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 the Sponsor.

9.4. Data sources

The details of the data sources, the BiKeR and the JuMBO registries are included in Section 9.2.

9.4.1. BiKeR registry

9.4.1.1. Operational procedures

The BiKeR registry collects data during routine clinical care of JIA patients. Treating physicians make decisions regarding clinical investigations, interventions or treatments which are not influenced by the registry. No other investigations or measures or additional visits other than what would be needed in routine clinical care are conducted for the BiKeR registry.

The BiKeR registry follows a standard procedure at all participating centers. Physicians are provided with a registry kit that includes the registry study protocol, paper-based structured CRFs including parental informed consent (IC) and patient assent forms, AE reporting form, serious adverse event (SAE) and pregnancy forms and drug discontinuation forms. Patients are evaluated at enrollment after the IC is signed and at months 3, 6 and every 6 months thereafter by treating physicians.

At the enrollment visit (baseline), the treating physician examines the health status of the patient at their office and completes the baseline CRF. The diagnosis, date of symptom onset, any past treatments, concomitant diseases, global assessment of current disease activity, 72-joint count, and the details of current biologic and non-biologic medication use are recorded on the CRF.

The patient is prospectively monitored via regular scheduled visits in usual clinical practice. At each visit, the physician examines the patient and decides with the patient regarding treatment changes. The relevant information closest to the registry scheduled visit date will be used. The follow-up CRFs include current disease activity, the date and reasons for change of medications, if applicable, as well as occurrence of AEs.

All CRFs filled out by patient/parent and by treating physician are sent to the registry coordinating center by mail or fax. Data administration is handled by trained personnel in the coordinating center. All documents are double checked for completeness and accuracy. Queries are sent in case of missing information or inconsistencies. The participating centers are monitored by trained personnel in regular intervals.

9.4.1.2. Informed consent

A written IC is collected at enrollment into the BiKeR registry according to the Declaration of Helsinki requirements. The BiKeR registry investigators or representatives explain the nature of the BiKeR registry to the parents or legal guardians and the patient, and answer all questions regarding this registry. Prior to inclusion in the BiKeR registry and any registry-related documentation being undertaken on the patient, the IC statement must be reviewed, signed and dated by the parents or legal guardians and the person who administers the IC. Patients are not reconsented during childhood (ie, <12 years of age). Patients older than 12 years are eligible to sign the patient information as well. A copy of the signed IC is given to the parents or legal guardians and the original is placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that IC is obtained prior to any registry-related documentation and that the patient has received a copy.

BiKeR receives data from the participating centers only in pseudonymized format (i.e., identity is encoded). Only the treating medical staff in the centers can identify the patient. On-Site monitoring is done by trained BiKeR staff who adhere strictly to data security and patient confidentiality regulations.

The BiKeR registry follows Good Clinical Practice (GCP). The registry is approved by the Ethics Committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg, Halle, Germany, and by the Ethics Committee of the Aerztekammer Nordrhein, Dusseldorf, Germany. The BiKeR registry protocol, any protocol amendments, the IC and all other forms of patient information related to the registry (e.g. advertisements used to recruit patients) and any other necessary documents have been reviewed by the Independent Ethics Committee.

9.4.2. JuMBO registry

JuMBO is a non-interventional long-term observation. The type of treatment administered and the conduct of individual therapy, including dosages, are determined by the treating physician only. Patients discontinuing drugs remain included in the register cohort, regardless of their new treatment.

The Program area Epidemiology and Health Services Research of Deutsches Rheuma-Forschungszentrum Berlin (DRFZ) is responsible for the conduct of JuMBO. The DRFZ team involved in JuMBO consists of the three PIs (a physician, an epidemiologist, and a statistician), a medical data manager, a study nurse (clinical trial manager), as well as medical/public health students. The physician is responsible for register supervision, coding of AEs and comorbidities, and compiling reports. The medical data manager, the study nurse and the students are responsible for the monitoring (e.g., contact with the BiKeR register center in St. Augustin and with rheumatology sites and other sites, contact with patients, organization of schedules, coding, dropout investigation) and maintaining consistency between all physicians and sites. The medical data manager, the nurse and the medical/public health students review the completed forms upon receipt and issue timely reminders to call patients for follow-up visits. If a patient is overdue by more than four weeks, they contact the patient by mail or a phone call up to 3 times. If a patient switches rheumatology sites, the new physician is asked by the patient (and optionally by the register management team) to complete the remaining forms.

All patients included in BiKeR are transferred to JuMBO around their 18th birthday and are reconsented. For this purpose, the register center St. Augustin provides the participating pediatric rheumatology sites with facility-specific lists of the identification (ID) numbers of those patients who will reach 18 years of age within the coming six months and with paper-based patient-specific IC forms. Before the patients leave pediatric rheumatology care, they are informed by pediatric rheumatologists about the follow-up register JuMBO and are asked whether they agree to participate in JuMBO.

Patients sign the IC form if they agree to participate in the registry, which is then sent to the DRFZ. At the time of enrollment, patients are also asked to consent to the transfer of pseudonymized data from BiKeR to JuMBO. After enrollment, the Register Coordinating Center (RCC) sends the documents to the patient by mail. The documents comprise a patient questionnaire, fee agreement, as

well as physician documents (physician questionnaire with precise instructions on filling out the questionnaire). The physician documents are sent to the patient in a sealed envelope, along with a request to pass the documents on to the physician currently caring for the patient. This patient-oriented register monitoring was chosen based on the following facts: (i) adult patients with JIA do not always remain in rheumatology care, (ii) doctors providing further treatment are not always known at the time when patients leave pediatric care, and (iii) young people change doctors relatively often, e.g., due to transient living situations and thus frequent relocation.

The documents (completed physician and patient questionnaires) are sent to the DRFZ by mail or fax as soon as they have been completed. Forms arriving at the RCC are reviewed promptly for completeness and plausibility. Queries are sent to the participating sites if there are missing data or implausible information-. When necessary, patients are contacted via mail, e-mail or telephone by the DRFZ to ensure the regular provision of follow-up information. Patients who do not indicate that they no longer wish to participate are contacted up to three times. Patients who have not sent a questionnaire for more than three years despite three reminders are counted as drop-outs. Individuals other than the patient are contacted only if the patient agrees. The sole purpose of contacting physicians other than the caring rheumatologist is to obtain or verify physician- and/or patient-reported SAEs or ESI.

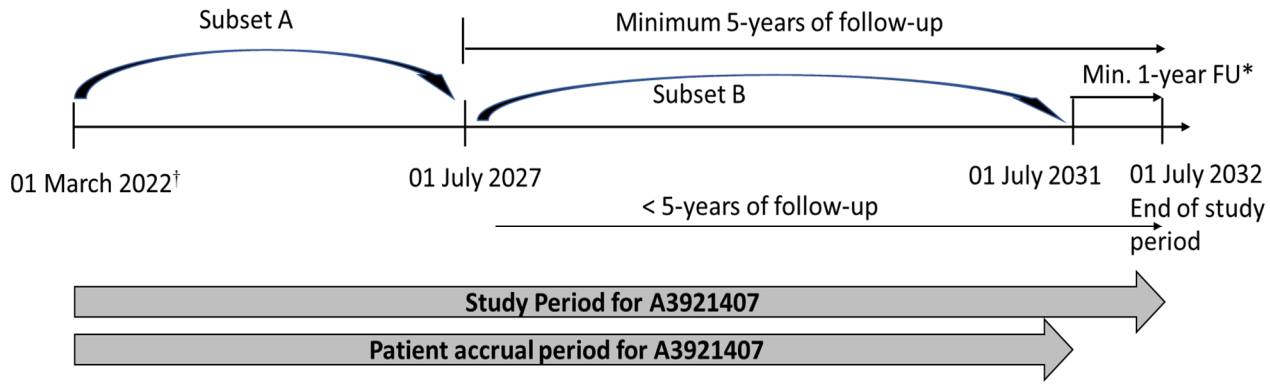
Both physicians and patients receive a financial incentive of 25 EUR per completed questionnaire (expense allowance for documentation) to ensure a participation rate as high as possible.

Patients will be observed for a maximum of 15 years after enrollment in BiKeR and a total of 5 years in JuMBO.

9.5. Study size

Due to the fact that tofacitinib is the first JAK inhibitor approved for JIA patients, there are no reliable data on the expected use of tofacitinib in JIA patients and the sample size will depend upon launch and market uptake of tofacitinib in Germany. This is as estimation study without pre-specified hypotheses. Sample size is based on estimating precision for IRs (ie, number of patients with event per 100 PY) for outcomes events of interest. All eligible patients enrolled in the BikeR and JuMBO registries following EU approval (August 2021) and product availability since 01 March 2022 through 01 July 2031 will be included, with no upper limit on the sample size.

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



*A minimum of 1-year follow-up will be included for ALL patients in the study.
† Product availability date for Germany is 01 March 2022.

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 01 March 2022 through 01 July 2027 (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 2032). Of these, some patients will have a follow-up greater than 5 years, for example, a patient who initiates tofacitinib or bDMARD on 01 July 2024 will be followed up for a period of 8 years until 01 July 2032. It should be noted that patients who initiate tofacitinib or approved bDMARD after 01 July 2027 (Subset B) will have an opportunity to contribute to a follow-up period of less than 5 years in the study.

It is expected to include approximately 300 patients in the tofacitinib cohort and 1000 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 is 4 years, resulting in a total of 1,200 PYs and 4,000 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.[18, 19, 20, 21, 22, 23, 24, 25] Precision estimates in terms of the 95% CI for the IRs for various combinations of IRs and PYs are provided below in **Table 1.**

Table 1. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and PYs

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
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
1200	0.005	0.00	0.31
1200	0.010	0.00	0.31
1200	0.050	0.00	0.46
1200	0.100	0.00	0.46
1200	0.500	0.18	1.09
1200	1.000	0.52	1.75
Comparator Cohort			
2000	0.005	0.00	0.18
2000	0.010	0.00	0.18

Table 1. Precision estimates in terms of the 95% CI for the incidence rates for various combinations of incidence rates and PYs

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	0.050	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
4000	0.005	0.00	0.09
4000	0.010	0.00	0.09
4000	0.050	0.01	0.18
4000	0.100	0.03	0.26
4000	0.500	0.31	0.77
4000	1.000	0.71	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 (300 patients in the tofacitinib cohort and 1000 patients in the comparator cohort) and presented in Table 2 below. The calculations make the following additional assumptions: (1) power = 80%, (2) 2-sided

α = 0.05, (3) 10-year total study duration (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 2. Minimum Detectable Hazard Ratios Comparing Tofacitinib-Treated Patients versus Comparator-Treated Patients with 80% Power, 2-sided α = 0.05, 10-Year Total Study Duration with 9 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†	300	1000	>14*
0.01†	300	1000	>14*
0.05†	300	1000	9.52
0.08†	300	1000	7.28
0.09†	300	1000	6.82
0.1§	300	1000	6.33
0.5§	300	1000	2.82
1.0¶	300	1000	2.18

*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 2, a study with a sample size of 300 patients in the tofacitinib cohort and 1,000 patients in the comparator cohort would detect a HR no less than 2.82 and 6.33 (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.[24] Similarly, a study with a sample size of 300 patients in the tofacitinib cohort and 1,000 patients in the comparator cohort would detect a HR no less than 2.18 (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.[25] Lastly, the background IRs of malignancies in JIA patients range from 0.005 to 0.09 per 100 PY, with IRs reported in studies conducted in Germany of 0.08 and 0.09 per 100 PY.[18,19,20,21,22,23] A study with sample size of 300 patients in the tofacitinib cohort and 1,000 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 the IR of 0.005 per 100 PY represents a background incidence of malignancy in JIA patients reported in a study conducted in Canada.[19] However, a study with sample size of 300 patients in the tofacitinib cohort and 1,000 patients in the comparator cohort would detect a HR no less than 9.52 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. [18,20] Furthermore, a study with sample size of 300 patients in

the tofacitinib cohort and 1,000 patients in the comparator cohort would detect a HR no less than 7.28 and 6.82 for IRs 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.[21,22,23] Of these 3 studies, two studies conducted by Barth et al (2017)[21] and Horneff et al (2016)[23] represent data from Germany, and of which the IR of malignancy of 0.09 per 100 PY reported by Horneff et al (2016)[23] is based on the data on malignancies in the BiKeR registry from the years 2000 to 2015. Therefore, it is reasonable to assume that the minimum detectable HRs will range from 6.82 to 9.52 corresponding to the background IRs of 0.05 to 0.09 per 100 PY in this study.

In addition to conducting a standardized analysis using 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 UK JIA Biologics Register is 285 and 250 patients, respectively and the anticipated sample of the comparator cohort in the other two studies using nationwide Swedish healthcare registers and the UK JIA Biologics Register is 860 and 750 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) 10-year total study duration in this study (9-years patient uniform accrual, and minimum 1-year follow-up from the last enrolled patient) and 8-year total study duration in the studies using Swedish HealthCare registers and the UK JIA Biologics register (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. 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 9/7 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

Table 3. 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 9/7 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

*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, 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.[24] 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.[25] 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.[19] However, the 3 PASS with a total sample size of 835 patients in the tofacitinib cohort and 2,610 patients in the comparator cohort in total 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.[18, 20] 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.[21,22,23] 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 [18, 21, 23]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

BiKeR registry

The BiKeR registry supplies paper CRFs to the participating study centers. CRFs must be completed for each patient enrolled in this registry. All CRFs must be legible and completed in indelible ballpoint ink. Any necessary corrections are made by drawing a single line through the incorrect entry and writing in the revision, and must be initialed and dated by the investigator or his/her designee. Data are not to be obliterated by blacking out, correction fluid, or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g. transcription error) should accompany the change. The original of the CRFs remains with the investigator, a copy of the CRF is faxed or posted to the BiKeR registry.

All paper CRF data are double entered by the BiKeR staff. All original forms are stored. Each form is scanned as a pdf file, which is placed on a secured server located in a hospital-based information center. Security and backups are under the responsibility of the information technology (IT) department of Asklepios Gesellschaft mit beschraenkter Haftung (limited company).

Data are coded in a standard way for input into the database. For example, sex is coded as: 1=male, 2= female; JIA subcategories are recorded as numbers from 1 to 7; Medications (active ingredient) have a numerical code; Dates (date of birth, disease onset) are recorded in date format; Absolute values are recorded for disease activity parameters (number of active joints, JADAS, VAS). Comorbidities and AEs are coded according to MedDRA coding system and each AE receives a coded number. Data are entered into a Microsoft Access database and transferred to SPSS (Statistical Package for the Social Sciences, IBM Software) database for statistical analysis.

JuMBO registry

Microsoft Office ACCESS version 2016 is used for data management. Statistical analyses are performed using SAS version 9.3 or higher. The contact information of patients and their physicians are entered into an ACCESS database (ACCESS I). Data from the questionnaires are separately entered into another ACCESS database (ACCESS II). Personal data such as names, addresses and telephone numbers are kept strictly separate from the questionnaire data. Patients' names, addresses and telephone numbers are disclosed to the register-coordinating office only for monitoring purposes. The personal details are entered by medical/public health students and data manager. The information is entered into the computer that are protected by two passwords and there is double data entry followed by validation of information. The server rooms are located in the basement of the DRFZ. They are secured by their own access system. The questionnaires contain a serial patient ID number that is allocated to each subject who signed the informed consent form for JuMBO. This ID number is different from the patient code used in BiKeR and is not based on personally identifying information. The IC form and the patient questionnaires (paper copies) are also kept at the DRFZ.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined 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 SAS, version 9.4 or higher (SAS Institute Inc., Cary, NC). All analyses will be carried out under the direction of Jens Klotsche, the leading statistician from the JuMBO registry.

The interim analysis will consist of descriptive comparisons of baseline characteristics of the 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 and comparator cohorts.

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.

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.[26] Under this approach, follow-up for each cohort starts at 6 months after the index date until the first occurrence 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 SAP will be used across the 4 registers (ie, BiKeR, JuMBO, UK JIA Clinical Register and nationwide Swedish healthcare registers). Analyses will be carried out using the data from BiKeR and JuMBO registries separately. Data will then be pooled from both registries (ie, BiKeR and JuMBO) on patient level using the BiKeR ID and verified using sex and birth date.

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

9.8.1. BiKeR registry

Quality control is performed in multiple steps. Plausibility checks are done at data input, data transfer, and at regular intervals through automated programs.

9.8.2. JuMBO registry

There are several steps for quality control: i) the questionnaires are checked for completeness, plausibility and relevant AEs upon arrival by fax; ii) the questionnaire data are checked again by two independent members of the monitoring team, who enter the data into two separate ACCESS data tables; and iii) both data tables are synchronized and checked for discrepancies. The questionnaire data are approved for statistical analyses in the case of no discrepancies. Database access is limited to authorized persons. Half-yearly data sets, which are thoroughly checked again for plausibility and completeness, are created for analyses. In addition, BiKeR and JuMBO mutually check data and report discrepancies. Further details on quality control will be included in the SAP.

Standard operating procedures govern the process of monitoring and data coding, entry, handling, cleaning, and analyses. The whole process of data monitoring, entry and cleaning (including query resolution) is protocolled.

The physician is responsible for supervising the register, coding AEs and compiling reports. Reported events are checked for plausibility, and in the case of uncertainty, verification is sought by collecting further event-related information.

The register management team is supported by a scientific advisory board that is shared with BiKeR. The scientific advisory board is appointed by the PIs in consultation with the executive board of the Society for Pediatric Rheumatology, in each case for three years. Re-nomination is possible. The advisory board’s duties include regular reviews of safety reports and consultations in the case of serious events.

9.9. Limitations of the research methods

This study is designed to monitor the safety of tofacitinib within the clinical practice setting utilizing the BiKeR and JuMBO registries. Despite the strengths of the registries, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling and endpoint misclassification, 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 may not be exclusively contemporaneous to tofacitinib treated patients. 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 concern within the observational setting due to less stringent monitoring of study outcomes relative to clinical trials. While the BiKeR and JuMBO registries have an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation.

Fourth, this study will follow patients for a period of up to 10 years from initiation of tofacitinib and approved bDMARDs. Conclusions may not be generalizable outside of the 10-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 10 years, in which case the 10-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.

Lastly, conclusions from this study may be limited to the EU population of JIA patients. 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 both registries.

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 final study report will be posted on EU PAS register. The interim and final study reports will be submitted to regulatory authorities. Data may be used in regulatory communications external to Germany 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.

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14. LIST OF TABLES

15. LIST OF FIGURES

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]

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	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:* (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

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	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 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

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	PT | Cardiac death PT | Cardiac failure congestive PT | Sudden cardiac death PT | Pulmonary embolism
Hypersensitivity	HLGT | Allergic conditions HLT | Allergic conditions NEC 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, BMI z-scores, and Tanner stage assessment. 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

Outcomes of Interest	MedDRA/SMQ level | MedDRA Term(s)/SMQ (MedDRA version 25)
	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 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

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 German Biologics in Pediatric Rheumatology Registry (BiKeR) and Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registries

EU PAS Register® number: pending registration
Study reference number (if applicable): A3921407

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

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

Comments:

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

[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 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
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, 9.2.3
4.2.2 Age and sex	☒	☐	☐	9.2.3
4.2.3 Country of origin	☒	☐	☐	9.1, 9.2.3
4.2.4 Disease/indication	☒	☐	☐	9.1, 9.2.3
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)	☒	☐	☐	9.2.3, 9.2.4

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?	☒	☐	☐	9.2.3.1.2, 9.2.3.2.2

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)	☐	☐	☒	No validation studies are planned.
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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2.1, 9.2.2, 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)	☒	☐	☐	9.2.1, 9.2.2, 9.3.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
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:				
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)	☒	☐	☐	9.4, 9.6, 9.7

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

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
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:

This section is not applicable for this study as this is the original protocol of the study.

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

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