NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	Characterization and outcomes follow up of patients with rheumatoid arthritis initiating tofacitinib: A retrospective, observational PASS using the British Society of Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)
Protocol number	A3921448
Protocol version identifier	v 1.0
Date	19th March 2024
EU Post Authorization Study (PAS) register number	
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-004
Procedure number	*If applicable, Agency or national procedure number(s), e.g., EMA/X/X/XXX (confirm with Pfizer EU/EEA or UK regulatory colleague).*
Marketing Authorization Holder(s)	Pfizer Europe
Joint PASS	No
Research question and objectives	**Research question:** What are the baseline characteristics, continuation and efficacy outcomes for adult patients with Rheumatoid Arthritis (RA) initiating tofacitinib in the UK? **Objectives:** 1. To assess the feasibility, completeness and quality of the datacut from the BSRBR-RA register to address the research question and subsequent objectives 2. To describe baseline characteristics for RA patients initiating

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	tofacitinib in the UK and compare to a TNFi cohort 3. To assess and quantify the proportion of RA patients who exhibit specific co-morbidities at baseline initiating tofacitinib 4. To describe the change in disease activity and pain scores from baseline to 36 months post tofacitinib initiation and compare to a TNFi cohort 5. Assess continuation of tofacitinib from baseline across 36 months and stratify by bio-experienced and bio-naïve populations
Country(ies) of study	United Kingdom
Author	Redacted

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Redacted
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Adalimumab
bDMARD	Biologic disease-modifying anti-rheumatic drugs
BSc	Bachelor of Science
BSR	British Society of Rheumatology
BSRBR-RA	British Society of Rheumatology Biologics register rheumatoid arthritis
BID	Twice daily
cm	Centimetres
COPD	Chronic Obstructive Pulmonary disease
CRP	C reactive protein
csDMARDs	Conventional synthetic disease modifying anti rheumatic drugs
DAS	Disease activity score
DMARD	Disease modifying anti rheumatic drug
ETA	Etanercept
ESR	Erythrocyte sedimentation rate
EU	European Union
HAQ	Health assessment questionnaire
IFN	Infliximab
IL	Interleukin
JAKi	Janus Kinase inhibitor
kg	Kilogram

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Abbreviation	Definition
Ltd	Limited
MI	Myocardial Infarction
NICE	National institute of clinical excellence
PASS	Post-authorisation safety study
PhD	Doctor of Philosophy
mg	milligram
MI	Myocardial Infarction
MRes	Master of Research
RA	Rheumatoid Arthritis
TB	Tuberculosis
TNFi	Tumour necrosis factor inhibitor
UK	United Kingdom
VAS	Visual analogue scale

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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Country Coordinating Investigators

Not Applicable.

4. ABSTRACT

Title: Characterisation and outcomes follow up of patients with rheumatoid arthritis initiating tofacitinib: A retrospective, observational PASS using the British Society of Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA).

Version: Final Protocol (v 1.0)

Date: March 2024

Rationale and background:

Janus kinases (JAK) are a family of cytoplasmic non-receptor tyrosine kinases that transduce cytokine signalling through the JAK-STAT pathway, regulating the transcription of inflammatory genes.[1] Small molecule inhibitors targeting JAKs (JAKi) have been developed to treat numerous inflammatory conditions, including rheumatoid arthritis (RA). Tofacitinib was approved in the European Union (EU) in March 2017 at a dose of 5 mg administered twice daily (BID) for the treatment of adult patients with moderately to severely active RA who have responded inadequately to, or who are intolerant to, one or more disease modifying antirheumatic drugs (DMARDs). As an exploratory, pilot study, this aims to (1) assess baseline characteristics, (2) assessment of continuation and (3) efficacy outcomes in a UK specific tofacitinib-initiating rheumatoid arthritis population.

Research Question: What are the baseline characteristics, continuation and efficacy outcomes for adult patients with Rheumatoid Arthritis initiating tofacitinib in the UK?

Objectives:

1. To assess the feasibility, completeness and quality of the datacut from the BSRBR-RA register to address the research question and subsequent objectives
2. To describe baseline characteristics for patients initiating tofacitinib in the UK and compare to a TNFi cohort
3. To assess and quantify the proportion of patients who exhibit specific co-morbidities at baseline initiating tofacitinib and compare to a TNFi cohort
4. To describe the change in disease activity and pain scores from baseline to 36 months post tofacitinib initiation and compare to a TNFi cohort
5. Assess continuation of tofacitinib from baseline across 36 months and stratify by bio-experienced and bio-naïve populations

Study design: This exploratory, voluntary, pilot PASS study uses data from the existing BSRBR-RA (an ongoing, prospective, observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use) supplied to Pfizer as part of the ongoing commitment PASS study A3921312.

Population: The study population will comprise all patients with RA enrolled within BSRBR-RA who receive tofacitinib following EU approval and marketing, with a data cut off of November 2021. For some objectives, one comparator cohort of patients within BSRBR with active RA at cohort entry will be used. This comparator cohort consists of RA patients initiating TNFi.

Variables: The study variables include baseline characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies), drug survival outcomes (ie. Period of time patients remain on tofacitinib from initiation, and reason for discontinuation), efficacy outcomes of interest including but not limited to DAS28, ESR, CRP, tender and swollen join counts and pain VAS.

Data sources: BSRBR collects core baseline data, including patient demographics and disease characteristics, which are collected by the recruiting clinician using a standardized form. In addition, some BSRBR personal and medical information are obtained directly from each patient recruited (eg, smoking history, alcohol consumption, and work status).

Study size: This is an exploratory, pilot, descriptive study without pre-specified statistical hypotheses and is unpowered. The sample size available in the BSRBR-RA dataset up to 30 November 2021 is 125 tofacitinib initiated patients, and 2231 TNFi initiated patients.

Data analysis:

- Descriptive comparisons of baseline clinical, demographic and comorbidity status between the tofacitinib and TNFi RA cohorts.
- Describe and quantify the proportion of patients who exhibit specific co-morbidities at baseline initiating tofacitinib and compared to TNFi RA cohorts.
- Descriptive analysis of tofacitinib continuation from baseline, stratified by bio-naïve and bio-experienced populations. Reason for discontinuation to be described.
- Descriptive comparison of disease activity and pain scores at baseline 6 and 12 monthly follow-ups for tofacitinib and TNFi cohorts

Milestones: A final study report will be provided XX months after study initiation.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Start of data collection	N/A
End of data collection	October 2022
Registration in the EU PAS register	March 2024
Final study report	April 2024

7. RATIONALE AND BACKGROUND

RA is a chronic and systemic inflammatory disease, with an estimated 17.6 million people with RA worldwide, which is forecast to increase to 31.7 million by 2050.[2] Globally, the age-standardised prevalence rate is 208.8 per 100,000 population, which increased 14.1% between 1990 and 2010.[2] In England, recent estimates suggest a prevalence rate of 29.4 per 100,000 person-years.[3] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity in addition to patients experiencing a broad range of co-morbidities.

Tofacitinib was the first oral JAK inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs.[4] Tofacitinib reduces the production of proinflammatory mediators by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA. Unlike biological therapies, such as tumour necrosis factor (TNF) inhibitor (TNFi) and anti-interleukin (IL)-6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines. Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity relative to other kinases in the human genome. In March 2017, XELJANZ® (tofacitinib citrate) was approved in the EU at a dose of 5 mg administered twice daily (BID) for the treatment of adult patients with moderately to severely active RA who have responded inadequately to, or who are intolerant to, one or more DMARDs.

Whilst numerous studies have investigated tofacitinib use in RA patients at a regional level (eg,: European, USA), to our knowledge, no studies thus far have assessed baseline characteristics, efficacy and continuation outcomes in a UK specific cohort of RA patients initiating tofacitinib. This study therefore serves to fill this knowledge gap. Similar studies have been conducted for other JAK's with market authorization in the UK.[5] The data source for this study is part of the EMA-dictated PASS study for tofacitinib (A3921312). Whilst the majority of the study does not aim to collect safety-related data, one objective is to provide data on drug survival of tofacitinib, which may partly be related to discontinuation due to adverse events.

This non-interventional study is designated as a voluntary PASS and is conducted voluntarily by Pfizer.

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8. RESEARCH QUESTION AND OBJECTIVES

Research Question: What are the baseline characteristics, continuation and efficacy outcomes for adult patients with Rheumatoid Arthritis initiating tofacitinib in the UK?

Objectives:

1. To assess the feasibility, completeness and quality of the datacut from the BSRBR-RA register to address the research question and subsequent objectives
2. To describe baseline characteristics for RA patients initiating tofacitinib in the UK and compare to a TNFi cohort
3. To assess and quantify the proportion of RA patients who exhibit specific co-morbidities at baseline initiating tofacitinib and compare to a TNFi cohort
4. To describe the change in disease activity and pain scores from baseline to 36 months post tofacitinib initiation and compare to a TNFi cohort
5. Assess continuation of tofacitinib from baseline across 36 months and stratify by bio-experienced and bio-naïve populations

9. RESEARCH METHODS

9.1. Study Design

This voluntary, exploratory, pilot PASS study uses data from the existing BSRBR-RA (an ongoing, prospective, observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use) supplied to Pfizer as part of the ongoing commitment PASS study A3921312.

All objectives of the study will be assessed in RA adult patients initiating tofacitinib in the UK since marketing authorization and UK launch of the product (fully available from January 2018). Baseline characteristics and efficacy outcomes in this cohort will be compared to an RA TNFi comparator cohort. This TNFi cohort are patients with active RA registered within 6 months of starting a TNF inhibitor as their first biologic. Recruitment to this cohort started in 2010 and is ongoing. All comparisons will be made with the overall TNFi class. Data cut off for both cohorts are November 2021.

This study uses secondary data, is descriptive and therefore has no hypotheses, no a priori hypotheses or sample size calculations. Data capture and follow-up methods are the same for all cohorts within the BSRBR-RA.

9.2. Setting

The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the UK. Initially, the main focus was on the study of the safety profile of the first three TNFi agents (ie, ADA, ETA and INF) as a class and as individual therapies. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies as they receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real-world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population. Unique features of BSRBR-RA include recruitment and collection of data from parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries. Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections, and malignancies. All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053). External validity, ie, generalizability to RA patients who are not enrolled in the register, is maximised by encouraging physicians to enroll every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

This study will consider two cohorts of patients:

1. Patients with active RA registered within 6 months of initiating tofacitinib. Recruitment to this cohort started at the time of UK marketing authorization for tofacitinib (2017) and is ongoing.

2. TNFi-exposed patients with active RA registered within 6 months of starting an anti-TNF biologic as their first biologic. Recruitment to this cohort started in 2010 and is ongoing. Patients enrolled in the TNFi-cohort who later initiate tofacitinib are eligible for subsequent enrolment in the tofacitinib-exposed cohort. Per national prescribing restrictions, patients were not prescribed TNFi and tofacitinib concurrently. All comparisons will be made with the overall TNFi class and not individual therapies.

The dataset to be analysed for the present study is an annual dataset with a cut off of 30 November 2021, dated and supplied in March and October 2022, respectively, which is provided to Pfizer as part of the commitment PASS study A3921312. Data to be used was retrieved from tofacitinib and/or TNFi BSRBR annual dataset dated March 2022 (data cut-off 30th November 2021, data collection from time of marketing authorization in the UK for tofacitinib (2017), and from 2010 for TNFi).

The term “registered” patient refers to all patients who register with the BSRBR-RA and upon starting their biologic/biosimilar/other targeted therapy and complete a clinical and patient baseline form. If a patient switched from their registered drug to a new biologic/biosimilar/other targeted therapy, they were usually encouraged to re-register prompting the completion of a new baseline

form to identify patient and disease characteristics at the start of their new therapy. These patients would also count as "registered" patients.

However, in some cases patients will switch biologic/biosimilar/other targeted therapy and not re-register in the study. These patients are referred to as "switchers". This is because, whilst BSRBR continues to follow-up them for safety events, BSRBR does not receive new baseline forms with the updated patient and disease characteristics at the point of starting their new therapy. Therefore "switchers" are not included in this study.

9.2.1. Inclusion Criteria

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

Section 9.2.1: Inclusion Criteria Tofacitinib-Exposed Cohort

- Eligible for BSRBR-RA.
- Initiation of tofacitinib, regardless of prior therapy (within 6 months of register enrolment).

Section 9.2.1. Inclusion Criteria Inclusion Criteria: TNFi-Exposed Cohort

- Eligible for BSRBR-RA.
- Initiation of a TNFi (within 6 months of register enrolment).

Patients who switched from a TNFi to tofacitinib, and did not re-register to BSRBR-RA are not included, due to the lack of baseline data obtained.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

The study variables include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies), specific co-morbidities of interest at baseline, efficacy outcomes at baseline, 6 and 12 month follow up, and continuation of tofacitinib from baseline.

9.3.1. Baseline Data

- Sex
- Age
- Current weight (kg)
- Current height (cm)
- Years of disease duration

- Systolic pressure
- Diastolic pressure
- Current/history of hypertension
- Current/history of angina
- Previous MI
- Previous Stroke
- Epilepsy
- Asthma
- COPD
- Current/history of peptic ulcer
- Current/history of liver disease
- Current/history of renal disease
- Current/history of demyelination
- Current/history of diabetes
- Current/history of hyperthyroidisim
- Current/history of depression
- Current/history of cancer
- Current smoker
- Past smoker
- Current/history of smoking
- Tender Joint count
- Swollen joint count
- ESR

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- CRP
- Patient global assessment VAS
- DAS28 total score
- HAQ score
- Prior exposure to bDMARD therapy

9.3.2. Outcome Measures

- Tender Joint count
- Swollen joint count
- ESR
- CRP
- Patient global assessment VAS
- DAS28 total score
- Proportion of patients remaining of tofacitinib at 6 monthly intervals (tofacitinib cohort only)
- Time to discontinuation following tofacitinib initiation (tofacitinib cohort only)
- Reason for stopping drug (tofacitinib cohort only)

9.4. Data Sources

The dataset to be analysed for the present study is an annual dataset with a cut off of 30 November 2021 which is provided to Pfizer as part of the commitment PASS study A3921312. Data to be used was retrieved from tofacitinib and/or TNFi BSRBR annual dataset dated March 2022 (data cut-off 30 November 2021, data collection from time of marketing authorization in the UK for tofacitinib (2017), and from 2010 for TNFi).

The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the UK. The register contains patients in the UK only. For the first 7-8 years the main focus was on the study of the safety profile of the first three TNFi agents. Since then, the further therapies including JAKi's have been added to the registry as approval has occurred in the UK.

The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies as they receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real-world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population.

Unique features of BSRBR-RA include recruitment and collection of data from parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries.[6] Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections,[7] and malignancies.[8,9] All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053).

Baseline

BSRBR is the source of core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardised form. In addition, some BSRBR personal and medical information reflect data obtained directly from each patient recruited (eg, on smoking history, alcohol consumption, and work status).

Follow-up

BSRBR data are the source of information on anti-rheumatic treatment, updated every 6 months/year. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of the DAS 28 is also collected.

BSRBR data include reports from patients contacted every 6 months for the first three years of their follow up period and asked to complete a patient diary which includes data about hospital admissions and new hospital referrals. Data collection instruments are distributed by post to patients and their physicians according to schedule. One attempt is made to follow-up non-responders. Non-responders at one follow up point are (unless further follow up is refused) contacted again at the next follow up point and all follow-up data since the last completed study follow-up is requested. Patients lost to follow up continue to be followed for death and cancer endpoints through the respective registers.

9.5. Study Size

This retrospective, descriptive study has no a priori hypotheses and is descriptive. Sample size calculations are therefore not applicable.

Within the data set to be analysed, baseline data are available for 125 subjects in the tofacitinib cohort, and 2231 in the TNFi arm.

9.6. Data Management

In BSRBR-RA data are collected via the hospital (at 6 monthly intervals for three years and annually thereafter) and patient questionnaires (at 6 monthly intervals for three years). Patient and physician assessments are sent via post to the study team at the University of Manchester who then enter the data into the study database. Pfizer are provided with an annual raw dataset as part of commitment PASS A3921312 study, with this specific dataset with data cut off 30 November 2021 to be analysed as part of the current study (A3921448).

9.7. Data Analysis

The dataset to be analysed for the present study is an annual dataset with a cut off of 30th November 2021 which is provided to Pfizer as part of the commitment PASS study A3921312. Data to be used was retrieved from tofacitinib and/or TNFi BSRBR annual dataset dated March 2022 (data cut-off 30th November 2021, data collection from time of marketing authorization in the UK for tofacitinib 2017, and from 2010 for TNFi). This dataset will be analysed by Pfizer UK Ltd using Microsoft Office and Graphpad Prism. This study uses secondary data, is descriptive and therefore has no hypotheses, no a priori hypotheses or sample size calculations.

All analyses are described below in Table 1 and will be descriptive in nature. No statistical analyses will occur. As described in Table 1, means, standard error of means and 95% confidence intervals will be provided for continuous variables when performing descriptive analysis of continuous data. Proportion of patients within cohorts may also be calculated. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures may be provided.

Any major modifications of the outlined analyses would be reflected in a protocol amendment.

Table 1. Summary of Planned Analyses

Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
Sex (M/F)	Tofacitinib & TNFi cohorts	2	Number, % male, % female	Excluded	Baseline
Age, (years)	Tofacitinib & TNFi cohorts	2	Mean ± 95% confidence intervals	Excluded	Baseline
Current height (kg) Current weight (cm)	Tofacitinib & TNFi cohorts	2	Mean ± 95% confidence intervals	Excluded	Baseline
Years of disease duration (years)	Tofacitinib & TNFi cohorts	2	Mean ± 95% confidence intervals	Excluded	Baseline
Systolic pressure (mmHg) Diastolic pressure (mmHg)	Tofacitinib & TNFi cohorts	2	Mean ± 95% confidence intervals	Excluded	Baseline
Current/history of hypertension (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of angina (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Previous MI (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Previous stroke (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Epilepsy (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Asthma (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
COPD (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of peptic ulcer (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline

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Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
Current/history of liver disease (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of renal disease (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of TB (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of demyelination (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of diabetes (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of hyperthyroidism (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of depression (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of cancer (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current smoker (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Ex-smoker (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Current/history of smoking (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline
Tender joint count (number)	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals, Mean ± 95% standard error of the mean	Excluded	Baseline & 6 monthly intervals
Swollen joint count (number)	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals, Mean ± 95% standard error of the mean	Excluded	Baseline & 6 monthly intervals
ESR (mm/hr)	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals, Mean ± 95% standard error of the mean	Excluded	Baseline & 6 monthly intervals
CRP (mg/dL)	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals, Mean ± 95% standard error of the mean	Excluded	Baseline & 6 monthly intervals
Patient global assessment VAS	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals, Mean ± 95% standard error of the mean, proportion of patients with VAS score score ≤ 20 and 40 (%)	Excluded	Baseline & 6 monthly intervals
DAS28 total score	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals, Mean ± 95% standard error of the mean, proportion of patients with DAS28 score ≤ 3.2 (%)	Excluded	Baseline & 6 monthly intervals
HAQ score	Tofacitinib & TNFi cohorts	2&4	Mean ± 95% confidence intervals	Excluded	Baseline & 6

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Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
					monthly intervals
bDMARD naïve (Y/N)	Tofacitinib & TNFi cohorts	2	Number, % of cohort	Excluded	Baseline
Patients continuing tofacitinib	Tofacitinib cohort	5	Number of continuing patients, number of discontinued patients, and proportion of patients (%) remaining on tofacitinib, stratified by bio-experienced and bio-naïve patients	Excluded	Baseline & 6 monthly intervals
Discontinuation due to inefficacy	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to remission	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to adverse event	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to other	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to unknown	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to death	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to clinical indication, switch to biosimilar	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to patient choice, switch to biosimilar	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to cost factors, switch to biosimilar	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Discontinuation due to other, switch to biosimilar	Tofacitinib cohort	5	Number, % of cohort	Excluded	As reported
Time to discontinuation, days	Tofacitinib cohort	5	Mean ± 95% confidence intervals. Calculated from start to stop date	Excluded	As reported
Time to discontinuation due to inefficacy, days	Tofacitinib cohort	5	Mean ± 95% confidence intervals. Calculated from start to stop date	Excluded	As reported
Time to discontinuation due to adverse event, days	Tofacitinib cohort	5	Mean ± 95% confidence intervals. Calculated from start to stop date	Excluded	As reported
Time to discontinuation due to other, days	Tofacitinib cohort	5	Mean ± 95% confidence intervals. Calculated from start to stop date	Excluded	As reported
Time to discontinuation due to death, days	Tofacitinib cohort	5	Mean ± 95% confidence intervals. Calculated from start to stop date	Excluded	As reported

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Data for any patient who stopped tofacitinib or a bDMARD in the respective cohorts will only be included up to the time point at which they stopped, and will be excluded from further timepoint analysis.

When assessing continuation of tofacitinib, the drug will be considered discontinued when a stop date was recorded in the BSRBR-RA, with no new start date recorded within the following 28 days.

9.8. Quality Control

Data used in this study are secondary use of data collected as part of the existing BSRBR, which has established quality control practices.

9.9. Limitations of the Research Methods

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilizing the BSRBR-RA, a well-established UK-based rheumatology register. Despite the strengths of the register, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint.

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 RA therapies and physical comorbidities.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing these events. The comparators in this study are not entirely contemporaneous to tofacitinib treated patients. Analysis will be unable to identify or control for any changes in rates due to changes in the treatment landscape.

The major limitation of the BSRBR-RA dataset is the significant degree of missing data post baseline. This therefore limits the n number analyzable at 6 and 12 month follow ups.

The term “registered” patient refers to all patients who register with the BSRBR-RA and upon starting their biologic/biosimilar/other targeted therapy and complete a clinical and patient baseline form. If a patient switched from their registered drug to a new biologic/biosimilar/other targeted therapy, they were usually encouraged to re-register prompting the completion of a new baseline form to identify patient and disease characteristics at the start of their new therapy. These patients would also count as “registered” patients. However, in some cases patients will switch biologic/biosimilar/other targeted therapy and not re-register in the study. These patients are referred to as “switchers”. This is because, whilst BSRBR continues to follow-up them for safety events, BSRBR does not receive new baseline forms with the updated patient and disease characteristics at the point of starting their new therapy. Such patients will not be included in this study due to lack of baseline data.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

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

All parties will ensure protection of patient personal data and will not include patient names or any other personal identifiable data on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

This study will use fully anonymized data from the existing BSRBR-RA, therefore patient consent is not applicable.

10.2. Patient Consent

As this study involves deidentified/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.

10.3. Patient Withdrawal

Not applicable. This study uses data from secondary data sources that include anonymized/deidentified structured data only.

10.4. Institutional Review Board (IRB)/ Ethics Committee (EC)

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

The analyses for this study will be completed using fully anonymized data. The data will not contain any patient identification information (eg, name), except for a unique number assigned.

The BSRBR-RA protocol is approved by the North West 5 Research Ethics Committee

(REC 00/8/053 with most recent approval amendment (#29) approval date of 22 September 2022).

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

A final study report will be provided at the end of data analyses, and manuscripts and conference publications based on the study results may be developed for external publication purposes.

13. REFERENCES

1. Banerjee, S., et al., JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects. Drugs, 2017. **77**(5): p. 521-546.

2. Collaborators, G.B.D.R.A., Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol, 2023. **5**(10): p. e594-e610.

3. Scott, I.C., et al., Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis epidemiology in England from 2004 to 2020: An observational study using primary care electronic health record data. Lancet Reg Health Eur, 2022. **23**: p. 100519.

4. Walker, J.G. and M.D. Smith, The Jak-STAT pathway in rheumatoid arthritis. J Rheumatol, 2005. **32**(9): p. 1650-3.

5. Edwards, C.J., et al., Characteristics of patients initiating treatment with baricitinib and outcomes at follow-up: analysis of BSRBR-RA Registry data. Rheumatology (Oxford), 2023. **62**(10): p. 3400-3408.

6. Elkayam, O. and K. Pavelka, Biologic registries in rheumatology: lessons learned and expectations for the future. Autoimmun Rev, 2012. **12**(2): p. 329-36.

7. Degli Esposti, L., et al., Persistence, switch rates, drug consumption and costs of biological treatment of rheumatoid arthritis: an observational study in Italy. Clinicoecon Outcomes Res, 2017. **9**: p. 9-17.

8. Mercer, L.K., et al., Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis, 2017. **76**(3): p. 497-503.

9. Silva-Fernández, L., et al., The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology (Oxford), 2016. **55**(11): p. 2033-2039.

14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15 October 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-authorization 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: Characterization and outcomes follow up of patients with rheumatoid arthritis initiating tofacitinib: A retrospective, observational PASS using the British Society of Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)

EU PAS Register® number:

Study reference number (if applicable):

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

Comments:

Secondary database study using data provided to Pfizer from the ongoing commitment PASS study A3921312

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
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)	☒	☐	☐	8
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)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

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)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (eg risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

No measure of association will be determined in this descriptive study. This is a secondary database study using

[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.

structured data, no reporting of adverse events is required for this protocol.

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:				9.2
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (eg event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Exposure is assumed after drug start date until drug stop date – definition of discontinuation given in section 9.2.

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? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.7
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7
5.4 Is intensity of exposure addressed? (eg, 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?	☒	☐	☐	

Comments:

Duration of tofacitinib exposure assessed, and efficacy outcomes measured at 6 monthly intervals.

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?	☒	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (eg precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☒	☐	

Redacted

Section 7: Bias	Yes	No	N/A	Section Number
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Purely descriptive study

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

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

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?	☒	☐	☐	9.2
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?	☐	☒	☐	

Redacted

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

This is a descriptive study. All data analysis components described in section 9.7.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (eg, 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?	☒	☐	☐	9.8

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? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

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?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	10.4
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

Fully anonymized data

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

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number

Redacted

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (eg, 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: Redacted

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Redacted