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NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1)
FINAL STUDY REPORT

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
Version identifier of the final study report	1.0
Date	SEPTEMBER 2024
EU Post Authorization Study (PAS) register number	EUPAS1000000102
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-004
Procedure number	Not applicable
Marketing Authorization Holder (MAH)	[redacted]
Joint PASS	No
Research question and objectives	**Research question:** What are the baseline characteristics, continuation and efficacy outcomes for adult

[redacted]

	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 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]

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Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	[redacted]
MAH contact person	[redacted]

[redacted]

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Refer to CT24-WI-GL15-RF06 Non-Interventional/Low-Interventional Study Type 1 Study Report/Manuscript Signatures, which clarifies the process for hard-copy and electronic signatures.

Appendix 2.1 PROTOCOL

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Not applicable

[redacted]

1. ABSTRACT (STAND-ALONE DOCUMENT)

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)

Date: XX July 2024

Name and affiliation of the main author: [redacted]

Keywords: tofacitinib, rheumatoid arthritis, efficacy, continuation

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. Small molecule inhibitors targeting JAKs (JAKi) have been developed to treat numerous inflammatory conditions, including rheumatoid arthritis (RA). Tofacitinib received marketing authorisation 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 study, this aimed to assess (1) baseline characteristics, (2) continuation and (3) efficacy outcomes in a UK specific tofacitinib-initiating adult rheumatoid arthritis population.

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

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.

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Setting: The BSRBR-RA is an existing registry, originally established in 2001 to study the safety of biologic therapies in RA patients living in the UK, which has been extended to other advanced therapies such as JAKi's. The register was used as a data source for the current study.

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

Variables and data sources: The study outcomes to be described 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. Patients analysed will be exposed to either tofacitinib, or anti-TNF therapy. 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).

Results: There were 125 and 2231 tofacitinib and anti-TNF initiating patients assessed in this study. At baseline, RA patients initiating anti-TNF or tofacitinib therapies exhibit existing comorbidities. At 12 months from initiation, tofacitinib and anti-TNF initiating patients both exhibit numerically reduced efficacy measures including the number of tender and swollen joint counts, ESR, CRP, pain VAS scores and DAS score. At 30 months post initiation, 76% of patients remained on tofacitinib, with the most common reason for discontinuation due to adverse events and inefficacy.

Discussion: In summary, this study descriptively adds to our knowledge regarding tofacitinib use in RA patients in the UK specifically, but should be interpreted with caution given the low patient numbers and high degree of missing data.

Marketing Authorization Holder(s): Pfizer Limited

Names and affiliations of principal investigators:

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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

[redacted]

Abbreviation	Definition
HAQ	Health assessment questionnaire
IFN	Infliximab
IL	Interleukin
JAKi	Janus Kinase inhibitor
kg	Kilogram
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

[redacted]

[redacted]

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Affiliation
Dr [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

4. OTHER RESPONSIBLE PARTIES

Not applicable

[redacted]

[redacted]

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	N/A	N/A	
End of data collection	01 October 2022	01 October 2022	
Registration in the EU PAS register	01 March 2024		
Final report of study results	01 April 2024		

[redacted]

[redacted]

6. 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 (1). Globally, the age-standardised prevalence rate is 208.8 per 100,000 population, which increased 14.1% between 1990 and 2010 (1). In England, recent estimates suggest a prevalence rate of 29.4 per 100,000 person-years (2). 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 (3, 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 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. In the UK, a registry-based post-authorisation safety study (A3921312) is being conducted by Pfizer as a category 3 commitment to the European Medicines Agency (EMA). That study aims to examine the rates of safety events of special interest in patients with RA treated with tofacitinib in relation to other advanced targeted therapies.

Whilst numerous studies have investigated tofacitinib use in RA patients at a regional level (eg,: European, USA), the current study aims to address baseline characteristics, efficacy and continuation outcomes in a UK specific cohort of RA patients initiating tofacitinib. 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 PASS and is conducted voluntarily by Pfizer.

7. 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

[redacted]

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

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

Please refer to appendix 2 for the final study protocol.

9.1. Study design

This voluntary, exploratory, pilot PASS study used 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 were 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 were 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 were made with the overall TNFi class. Data cut off for both cohorts was 30th November 2021.

This study used secondary data, was descriptive and therefore had no hypotheses, no a priori hypotheses or sample size calculations. Data capture and follow-up methods were 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.

9.3. Subjects

Since the current study used secondary data from the ongoing BSRBR-RA registry and A3921312 study, patient recruitment was not applicable. The population included patients with RA already enrolled in the register who met the criteria as described below. Tofacitinib-exposed patients included enrolled as new to the register at the point of starting tofacitinib, or if already registered, were registered at the time of starting tofacitinib.

[redacted]

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 were made with the overall TNFi class and not individual therapies.

9.3.1. Inclusion criteria

Patients met the inclusion criteria at baseline to be eligible for inclusion in the study:

9.3.1.1. Inclusion criteria: tofacitinib exposed cohort

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

9.3.1.2. Inclusion criteria: TNFi exposed cohort

- Eligible for BSRBR-RA
- Initiation of a TNFi therapy within 6 months of register enrolment

9.3.2. Exclusion criteria

There were no exclusion criteria for this study.

The dataset analysed for the present study is an annual dataset with a cut off of 30 November 2021, dated and supplied in March 2022, which is provided to Pfizer as part of the commitment PASS study A3921312. Data 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

[redacted]
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 due to the lack of baseline data.

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.

9.4. Variables

The study variables included 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.

9.4.1. 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

[redacted]

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

9.4.2. 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)

[redacted]

9.5. Data sources and measurement

The dataset analysed was an annual dataset with a cut off of 30th November 2021 which was provided to Pfizer as part of the commitment PASS study A3921312. Data 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 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 (ie, ADA, ETA and INF) as a class and as individual therapies. 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.

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

[redacted]

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 30th November 2021 to be analysed as part of the current study (A3921448)

9.6. Bias

Using the datasets provided by the BSRBR-RA as part of the committment PASS study A3921312, this study was designed to describe baseline characteristics, change in disease activity and pain score at follow up, and continuation of drug in RA patients initiating tofacitinib in the UK. Some analyses also compared to a TNFi cohort.

As a new therapy in the EU RA treatment landscape, it is possible that patients treated with tofacitinib may represent the most severe cases of disease, longer disease duration and multiple comorbidities. To somewhat address this, some analyses will be stratified based on previous DMARD exposure.

Misclassification of events may be a concern within the observational setting since less stringent monitoring occurs relative to clinical trials. Whilst the BSRBR-RA have established systems to identify and capture data, it is not feasible in this study to verify all events via source documentation.

9.7. Study Size

This retrospective, descriptive study had no a priori hypotheses and was descriptive. Sample size calculations were therefore not applicable.

Within the data set analysed, baseline data was available for 125 subjects in the tofacitinib cohort, and 2231 in the TNFi cohort.

9.8. Data transformation

The BSRBR-RA registry data are collected via hospital (at 6 monthly intervals for three years) and patient questionnaires (at 6 monthly intervals for three years). Patient and physician assessments are sent to the study team at the University of Manchester who then enter the data into the study database. No further data transformation was conducted during this study.

9.9. Statistical methods

9.9.1. Main summary measures

All analyses are described below and are descriptive in nature, conducted by Pfizer. No statistical analyses occured. As described below, means, standard error of means and 95% confidence intervals were provided for continuous variables when performing descriptive analysis of continuous data. Proportion of patients within cohorts were also calculated. Numbers and percentages were provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures may be provided. For summary measures and graphical data presentation, GraphPad Prism 9.5.1 was used.

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
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

[redacted]

Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
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 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

[redacted]

Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
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

9.9.2. Main statistical methods

All analyses were conducted by Pfizer, were descriptive in nature and therefore no statistical analyses occurred.

9.9.3. Missing values

Missing values were not included in the denominator count when computing percentages. Similarly, only the non-missing values were evaluated for computing summary statistics. No imputation methods were used.

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

None

9.10. Quality control

Data used in this study were secondary data collected from the existing BSRBR-RA registry, which has established quality control practices.

9.11. Protection of human subjects

Subject information and consent

This study involved data that exist in an anonymized structured format and contains no patient personal information.

As this study uses fully anonymized structured data from the existing BSRBR-RA registry, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patient by Pfizer is not required.

This was a secondary data collection study using full anonymized data and therefore informed consent was not applicable.

[redacted]

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

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

IRB/IEC review was not required for this study. NHS health research authority and IRAS submission was not required as post-marketing surveillance is not considered research.

The overall 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).

Ethical conduct of the study

The study was 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.

10. RESULTS

The results are presented in table 1 to table 4, and figure 1 to figure 4.

10.1. Participants

During the study period of 1st January 2001 to 30th November 2021, there were 125 and 2231 RA patients in the tofacitinib exposed cohort, and the anti-TNFi exposed cohort, respectively (Table 1). All 125 tofacitinib exposed patients were new registrations, or switched to tofacitinib and re-registered in the BSRBR-RA.

Cumulative number of registrations on Xeljanz (since 01/01/2001)	125
Cumulative number of registrations on anti-TNF (since 01/01/2001)	2231

Table 1: Number of registered RA patients on tofacitinib and anti-TNF in the BSRBR-RA registry at time of data cut off 30th November 2021. The term "registered" patient refers to all patients who register with the BSRBR-RA upon starting tofacitinib, or those who re-register following switching from another drug. Switched patients are those who switch to tofacitnib from another drug and do not re-register in the study - such patients are not included as baseline data is unavailable. Source: Excel files 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21'.

10.2. Descriptive data

The demographic characteristics of patients at baseline initiating tofacitinib or anti-TNF therapy in the BSRBR-RA registry up to 30th November 2021 are presented in Table 2.

10.2.1 Demographics

[redacted]

In both treatment groups, the majority of patients were female, (72.8% and 75.9% for tofacitinib and anti-TNF, respectively), with the anti-TNF cohort approximately 4 years older on average as compared to the tofacitinib cohort (mean 57.18, range 56.65-57.72 and mean 61.02, range 58.89-63.16, respectively). Duration since RA diagnosis was numerically higher in the tofacitinib cohort as compared to the biologic cohort (mean 14.47, range 12.66-16.28 and mean 8.999, range 8.604-9.395 respectively). Height, weight and blood pressure between groups was similar.

10.2.2 Health characteristics

Of the baseline comorbidities measured, smoking status (51.4% and 60.7% of the tofacitinib and anti-TNF cohorts, respectively), current or history of hypertension (33.6% and 29.7% of the tofacitinib and anti-TNF cohorts, respectively) and current/history of depression (20.8% and 21.4% of the tofacitinib and anti-TNF cohorts, respectively) had the highest frequencies in both cohorts. Comorbidity status of all those assessed are presented in table 2.

The tender joint count numbers were both numerically higher in the anti-TNF initiating cohort as compared to the tofacitinib cohort (mean 14.5, range 14.9-14.81; mean 11.23, range 9.850-12.61, respectively). A similar trend was seen for the swollen joint count (mean 8.54, 8.33-8.76; mean 7.12, range 6.307-7.936, respectively). ESR and CRP were numerically higher in the tofacitinib cohort (ESR mean 32.23, range 25.50-38.96; CRP mean 25.42, range 25.50-38.96) as compared to the anti-TNF cohort (ESR mean 30.26, range 29.06-31.45; CRP mean 21.87, range 20.31-23.42). Patient global assessment VAS, DAS28 total score and HAQ score were similar between the two cohorts.

10.2.3 Medication history

In the tofacitinib cohort, 30.89% of patients initiating tofacitinib were biologic naïve, whilst 99.3% of the biologic initiating cohort were biologic naïve.

	Tofacitinib		**Anti-TNF**	
		n number		n number
Demographic information				
Male, no. (%)	34 (27.2)		538 (24.1)	
Female, no. (%)	91 (72.8)		1693 (75.9)	
Age, years	61.02 (58.89-63.16)	125	57.18 (56.65-57.72)	2231
Age ≥ 65 years, no. (%)	53 (42.4)	125	710 (31.8)	2231
Current weight, kg	81.09 (75.28-86.90)	68	78.62 (77.74-79.50)	2025
Current height, cm	165 (161.0-169.2)	57	176.4 (160.2-192.6)	1686
Duration since RA diagnosis, years	14.47 (12.66-16.28)	121	8.999 (8.604 - 9.395)	2175
Systolic pressure	135.2 (130.1-140.3)	65	135.8 (134.9-136.7)	1939
Diastolic pressure	80.57 (77.74-83.40)	65	79.89 (79.37-80.40)	1937
Comorbidity status				
Current/history of hypertension, no. (%)	42 (33.6)	125	633 (29.7)	2231
Current/history of angina, no. (%)	3 (2.4)	125	98 (4.4)	2231
Previous MI, no (%)	4 (3.2)	125	73 (3.3)	2231
Previous stroke, no (%)	3 (2.4)	125	47 (2.1)	2231

Epilepsy, no. (%)	5 (4.0)	125	22 (1)	2231
Asthma, no. (%)	17 (13.6)	125	322 (14.4)	2231
COPD, no. (%)	9 (7.2)	125	139 (6.2)	2231
Current/history of peptic ulcer, no. (%)	5 (4.0)	125	75 (3.4)	2231
Current/history of liver disease, no. (%)	4 (3.2)	125	40 (1.8)	2231
Current/history of renal disease, no. (%)	2 (1.6)	125	58 (2.6)	2231
Current/history of TB, no. (%)	6 (4.8)	125	89 (4.0)	2231
Current/history of demyelination, no. (%)	1 (0.8)	125	8 (0.36)	2231
Current/history of diabetes, no. (%)	13 (10.4)	125	183 (8.2)	2231
Current/history of hyperthyroidism, no. (%)	6 (4.8)	125	82 (3.7)	2231
Current/history of depression, no. (%)	26 (20.8)	125	477 (21.4)	2231
Current/history of cancer, no. (%)	14 (11.2)	125	99 (4.4)	2231
Current smoker, no. (%)	11 (14.9)	74	386 (19.6)	1969
Ex-smoker, no. (%)	27 (36.4)	74	809 (41.1)	1969
Current/history of smoking, no. (%)	38 (51.4)	74	1195 (60.7)	1969
Disease characteristics				
Tender Joint count, no.	11.23 (9.850-12.61)	99	14.5 (14.19-14.81)	2109
Swollen Joint count, no.	7.12 (6.307-7.936)	99	8.54 (8.33-8.76)	2106
ESR	32.23 (25.50-38.96)	66	30.26 (29.06-31.45)	1658
CRP	25.42 (17.62-33.22)	62	21.87 (20.31-23.42)	1253
Patient global assessment VAS	70.72 (65.98-75.45)	95	73.29 (72.42-74.16)	2053
DAS28 total score	5.47 (5.179-5.654)	124	5.9 (5.905-5.994)	2225
HAQ score	1.663 (1.421-1.906)	36	1.54 (1.504-1.576)	1717
Prior and concomitant RA medications				
bDMARD naïve	38 (30.89)	123	2216 (99.3)	2231

Table 2: Baseline Characteristics for registered patients with Rheumatoid Arthritis in the BSRBR-RA tofacitinib and anti-TNF cohorts. Source: Excel files 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21'.

10.3. Outcome data

Not applicable.

[redacted]4

10.4. Main results

The analysis of all study endpoints was assessed in all 125 tofacitinib initiated patients with available data. For the anti-TNF cohort, study endpoints relating to baseline demographic information, disease activity and pain scores were analysed only. For some baseline demographic variables, disease activity and pain scores, data was not available for all patients at every timepoint, and therefore data are presented where available only. All results, especially those post 12 months are difficult to interpret given the variation in n number and degree of missing data for the latter timepoints for the tofacitinib cohort.

10.4.1 Disease activity scores

Disease activity scores comparing tofacitinib and TNFi exposed cohorts are provided in Figure 1 from baseline to 36 months. Due to the high degree of missing data post 12 months follow up, only data up to this timepoint will be discussed in text.

At 12 months follow up as compared to baseline, tofacitinib and TNFi cohorts exhibited numerically reduced ESR values (mean 16.13 vs 32.23 for tofacitinib and mean 18.93 vs 30.26 for TNFi at 12 months and baseline, respectively). Reduction in ESR at 12 months was similar between cohorts, but numerically lower for tofacitinib (mean 16.13 vs 18.93 for tofacitinib and TNFi, respectively).

Regarding CRP, both tofacitinib and TNFi cohorts exhibited numerically reduced values at 12 months as compared to baseline (mean 5.37 vs 25.42 for tofacitinib and 9.170 vs 21.87 for TNFi at 12 months and baseline, respectively), with tofacitinib values at 12 months numerically lower than those observed for TNFi (mean 5.370 for tofacitinib vs 9.170 for TNFi).

For both tofacitinib and TNFi cohorts, the number of tender joints were similarly lower at 12 months as compared to baseline (mean 4.64 vs 11.23 for tofacitinib and mean 4.596 vs 14.50 for TNFi at 12 months and baseline, respectively). Similar trends were observed for swollen joint counts (mean 2.21 vs 7.12 for tofacitinib and mean 2.24 vs 8.54 for TNFi at 12 months and baseline, respectively).

In terms of disease activity score (DAS), tofacitinib and anti-TNF cohorts exhibited similar reductions at 12 months as compared to baseline (mean 3.191 vs 5.417 for tofacitinib and mean 5.949 vs 3.459 for TNFi at 12 months and baseline, respectively). At 12 months, 48.4% of the anti-TNF cohort, and 46.7% of the tofacitinib cohort achieved a DAS score of ≤3.2.

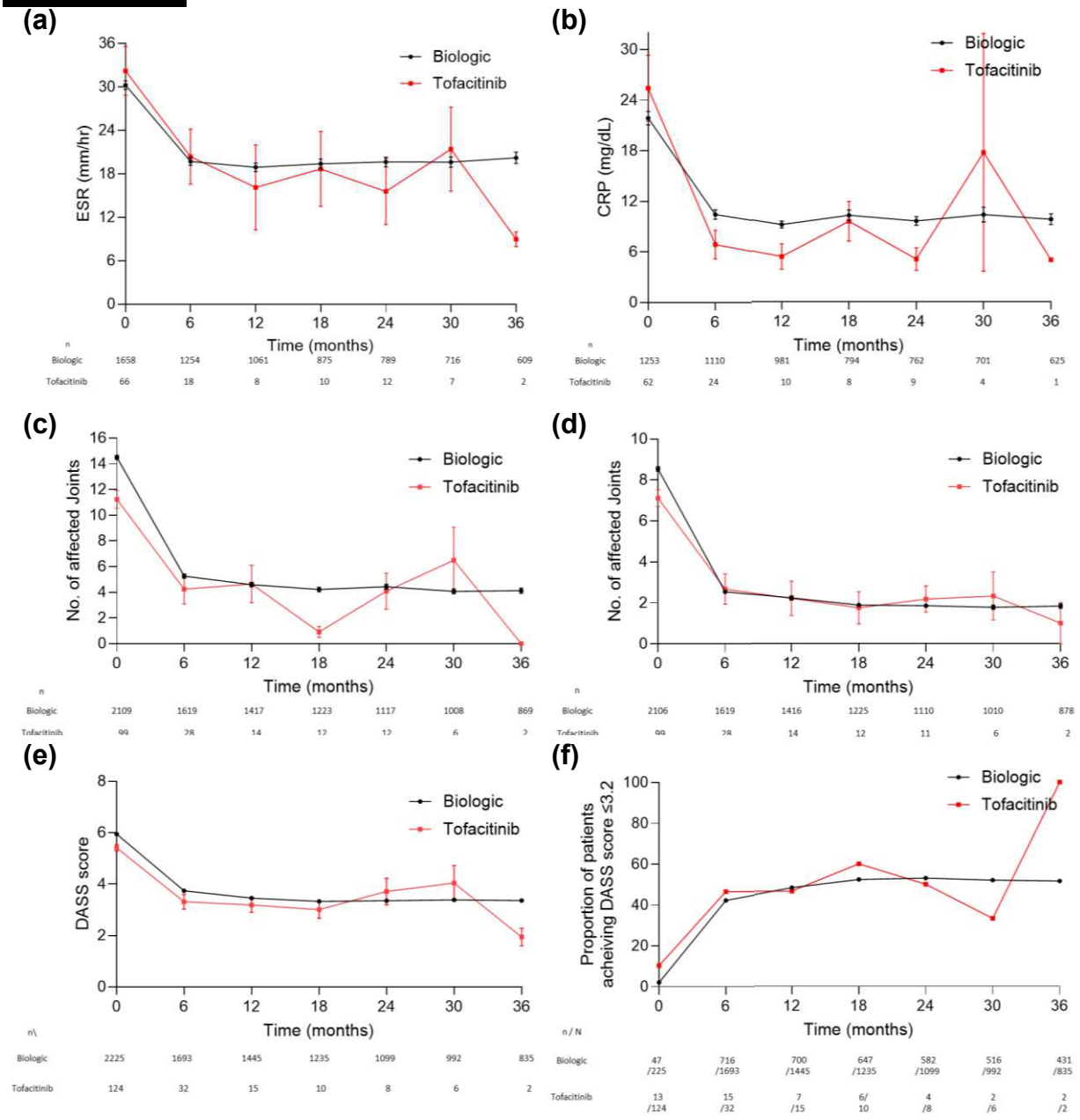

Figure 1: Disease activity scores from baseline and overtime following treatment initiation. Mean ± SEM comparing disease activity scores (a) ESR, (b) CRP, (c) tender joint count, (d) swollen joint count, (E) DASS score and (f) proportion of patients achieving DASS score of ⩽ 3.2 for RA patients on a bDMARD as compared to tofacitinib from baseline to 36 months. Datapoints presented for patients with scores available at specified timepoints only. Patients who discontinued either therapy were excluded from discontinuation timepoint. Source: Excel files 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21'.

10.4.2 Pain scores

Visual analogue scores at 12 months as compared to baseline were both lower with anti-TNF and tofacitinib therapy (mean 73.29 vs 39.60 for anti-TNF and 70.72 vs 44.5 for tofacitinib and mean 4.596 vs 14.50 at baseline and 12 months, respectively). At 12 months,

[redacted]

34.4% and 30% of patients on anti-TNF therapy or tofacitinib had a VAS score of ≤20. Additionally, at 12 months, 55.3% and 40% of patients on anti-TNF therapy or tofacitinib had a VAS score of ≤20.

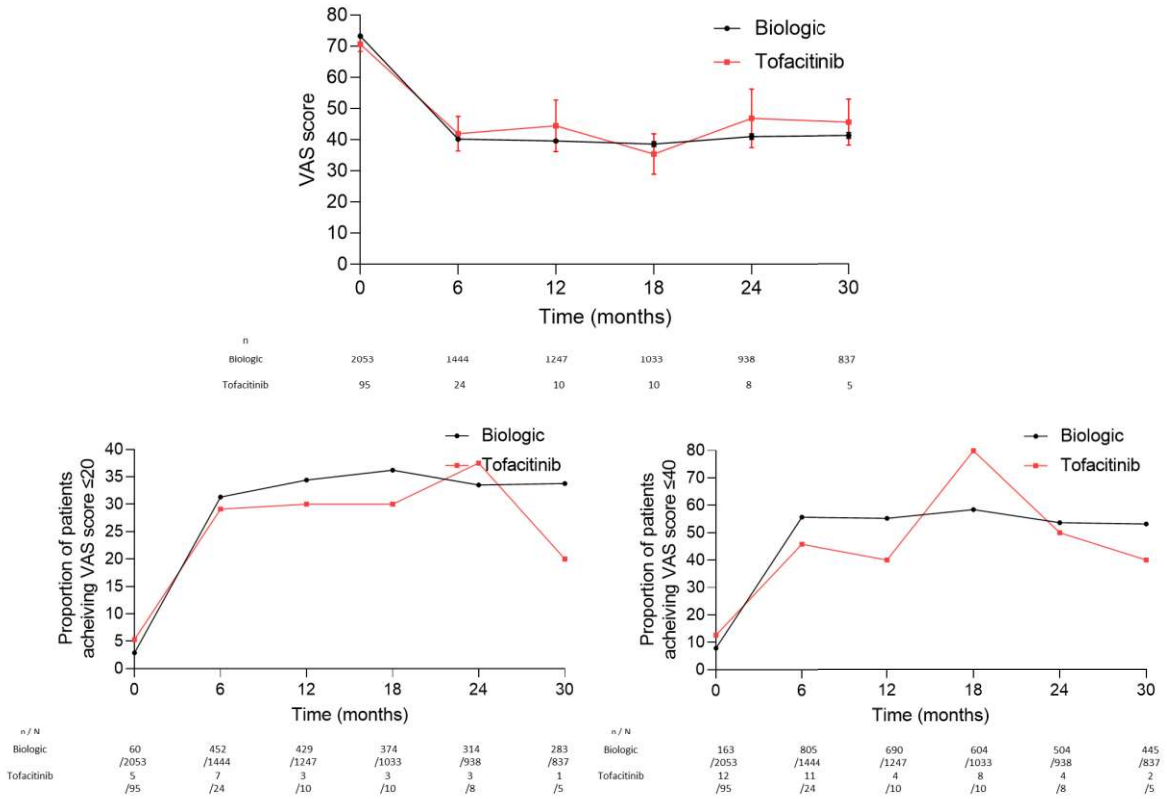

Figure 2: Pain scores from baseline and overtime following treatment initiation. Mean or mean ± SEM comparing pain scores (a) raw VAS score, (b) proportion of patients achieving VAS score of ⩽ 20, and (c) proportion of patients achieving VAS score of ⩽ 40 for RA patients on a bDMARD as compared to tofacitinib from baseline to 36 months. Datapoints presented for patients with scores available at specified timepoints only. Patients who discontinued either therapy were excluded from discontinuation timepoint. Source: Excel files 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21'.

10.4.3 Continuation

Tofacitinib continuation rates from baseline, through follow-up are presented in figure 3 and table 3. At 36 months post initiation, 76.0 % of patients remained on tofacitinib. Bio-naïve patients initiating tofacitinib had a numerically higher continuation rate as compared to those who had previously been exposed to a biologic (81.6 % vs 74.4 %, respectively).

[redacted]

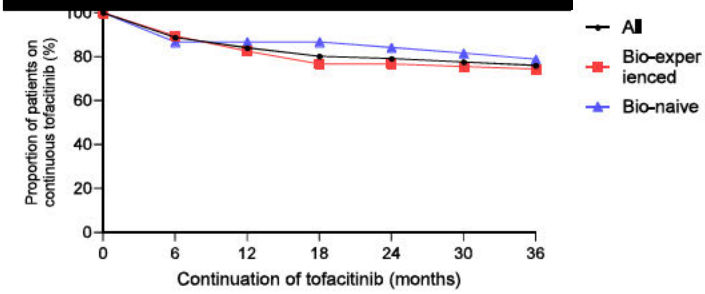

Figure 3: Tofacitinib continuation from baseline for the overall cohort. Proportion of RA patients at 6 monthly intervals from baseline who remain on tofacitinib. For those initiating tofacitinib, all patients, bio-experienced patients, and bio-naïve patients were stratified. The drug was considered to be discontinued when a stop date was recorded in the BSRBR-RA, with no new start date recorded within the following 28 days. Source: Excel file 'BSRBR Xeljanz 30.11.21'.

Timepoint	Total number of patients on tofacitinib at timepoint	Number of patients discontinued	Proportion of patients remaining on tofacitinib (%)
All patients			
Baseline	125		
6 months	111	14	88.8
12 months	105	6	84.0
18 months	100	5	80.2
24 months	99	1	79.2
30 months	97	2	77.6
36 months	95	2	76.0
Bio-experienced patients			
Baseline	86		
6 months	77	9	89.5
12 months	71	6	82.5
18 months	66	5	76.7
24 months	66	0	76.7
30 months	65	1	75.5
36 months	64	1	74.4
Bio-naive patients			
Baseline	38		

[redacted]

6 months	33	5	86.8
12 months	33	0	86.8
18 months	33	0	86.8
24 months	32	1	84.2
30 months	31	1	81.6
36 months	30	1	78.9

Table 3: Details of tofacitinib continuation and discontinuation from baseline to 36 months. Source: Excel file 'BSRBR Xeljanz 30.11.21'.

10.4.5 Reasons for discontinuation

Reasons for discontinuing tofacitinib (with no new start date recorded within the following 28 days) are listed in Table 4. Of those who discontinued, most did so due to an adverse event (67.7 %), followed by inefficacy (19.4 %), other (6.1 %) or death (3.1 %). Of those who discontinued for ≥28 days, the next primary drug recorded was 66.6% 'other biologic', 23.3% 'not reported' and 10% 'Xeljanz'.

Discontinuation	
Permanent discontinuations, no. (% total patients at baseline)	30 (24.0)
Inefficacy, no (% discontinuations)	6 (19.4)
Remission, no (% discontinuations)	0
Adverse event, no (% discontinuations)	21 (67.7)
Other, no. (% discontinuations)	2 (6.1)
Unknown, no (% discontinuations)	0
Death, no. (% discontinuations)	1 (3.1)
Clinical indication (switch to biosimilar), no. (% discontinuations)	0
Patient choice (switch to biosimilar), no. (% discontinuations)	0
Costs factors (switch to biosimilar), no. (% discontinuations)	0
Other (switch to biosimilar), no. (% discontinuations)	0

Table 4: Reasons for tofacitinib continuation. Table highlighting the raw number and proportion of patients discontinuing tofacitinib at any point after initiation. The drug was considered to be discontinued when a stop date was recorded in the BSRBR-RA, with no new start date recorded within the following 28 days. Source: Excel file 'BSRBR Xeljanz 30.11.21'.

The average time to discontinuation was 304.6 days. Patients who discontinued due to an adverse event discontinued quicker (226.4 days), whilst patients who discontinued due to inefficacy continued tofacitinib for longer (393.8 days).

[redacted]

Time to Discontinuation following tofacitinib initiation		
		n number
Time to discontinuation, days	304.6 (202.9.0-406.3)	30
Time to discontinuation due to inefficacy, days	393.8 (72.7-715.0)	6
Time to discontinuation due to AE, days	226.4 (131.4-321.4)	21
Time to discontinuation due to other, days	723.0 (-3407-4853)	2
Time to discontinuation due to death, days	574	1

Table 5: Time from tofacitinib continuation to discontinuation. Table highlighting the raw number and proportion of patients discontinuing tofacitinib at any point after initiation. The drug was considered to be discontinued when a stop date was recorded in the BSRBR-RA, with no new start date recorded within the following 28 days. Source: Excel file 'BSRBR Xeljanz 30.11.21'.

10.4.6 Risk factors

Of those patients initiating tofacitinib, 14.9% were current smokers, 36.4% were an ex-smoker, and 48.7% had never smoked. The proportion of patients exhibiting certain risk factors at baseline were assessed. Such risk factors considered included age ⩾65, history or current ASCVD (Hypertension, Angina, MI, Stroke), cancer, current or ex-smoker. Of those initiating tofacitinib, at baseline, 27.2%, 38.4%, 22.4%, 11.2%, and 0.8% had 0,1,2,3 or 4 of the selected risk factors, respectively.

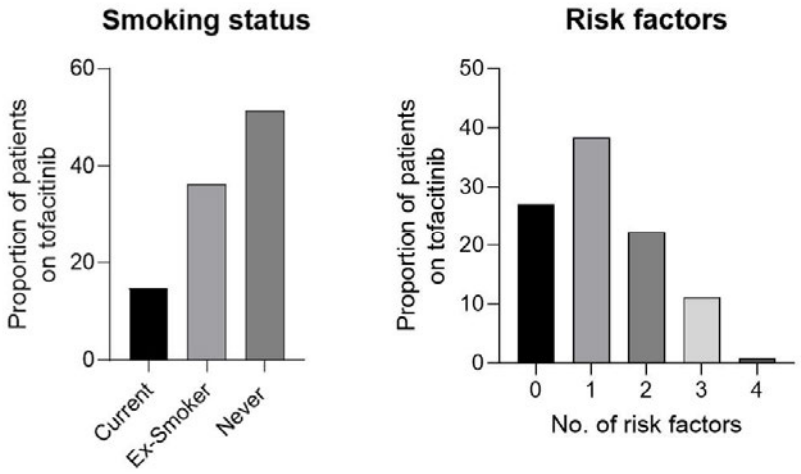

Figure 4: Proportion of patients with additional risk factors within BSRBR-RA registry treated with tofacitinib at baseline. (a) proportion of patients who initiated tofacitinib who are current smokers, ex-smokers or have never smoked. (b) proportion of patients who have shown number of risk factors. Risk factors assessed included: age ⩾65, History or current ASCVD (Hypertension, Angina, MI, Stroke), Cancer, current or ex-smoker. Excel file 'BSRBR Xeljanz 30.11.21'

10.5. Other analyses

None

[redacted]

10.6. Adverse events / adverse reactions

This study involved data that existed as structured data by the time of study start. In these data sources, individual patient data were not retrieved or validated, and it is not possible to link (ie: identify a potential associated 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) were not met.

11. DISCUSSION

11.1. Key results

This report describes baseline characteristics, efficacy outcomes and continuation rates for adult RA patients initiating either anti-TNF or tofacitinib in the UK. As of 30th November 2021, the cut off date for the data used with this study, there were 125 and 2231 tofacitinib and anti-TNF initiating patients, respectively. The following observations were made:

1. Limited conclusions can be drawn from this study, given the lower numbers of tofacitinib initiating patients at baseline (125), with follow up data further dramatically decreasing at each 6 monthly interval. Therefore all results should be considered with caution with restricted interpretation.

2. At baseline, RA patients initiating anti-TNF or tofacitinib therapies exhibit existing comorbidities.

3. At 12 months from initiation, tofacitinib and anti-TNF initiating patients both exhibit numerically reduced efficacy measures including the number of tender and swollen joint counts, ESR, CRP, pain VAS scores and DAS score.

4. At 30 months post initiation, 76% of patients remained on tofacitinib, with the most common reason for discontinuation due to adverse events and inefficacy.

11.2. Limitations

This study was designed to assess the utilisation 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.

[redacted]

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 were not included in this study due to lack of baseline data.

11.3. Interpretation

The low numbers of patients, and high degree of missing data in this study does not allow for accurate and reliable interpretation of results.

11.4. Generalizability

This study used data from BSRBR-RA which collects data from patients with RA living in the UK. Generalizability to patients with RA, who are not enrolled in the register is maximized by encouraging physicians to enroll all patients. However, the data set used had a large amount of missing data, with a low number of tofacitinib initiating patients captured in the registry and therefore the generalizability of the results should be interpreted with care.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

In summary, this study descriptively adds to our knowledge regarding tofacitinib use in RA patients in the UK specifically. Results should be interpreted with caution given the low number of tofacitinib patients within the study, and the high degree of missing data.

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[redacted]

15. LIST OF SOURCE TABLES AND FIGURES

Not applicable

[redacted]

Appendix 1

[redacted]

Appendix 2

Protocol

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	Characterisation and Outcomes Follow up of Patients With Rheumatoid Arthritis Initiating Tofacitinib: A Retrospective, Observational Post-authorisation safety study (PASS) Using the British Society of Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA)
Protocol number	A3921448
Protocol version identifier	v 1.0
Date	22 July 2024
EU Post Authorization Study (PAS) register number	EUPAS1000000102
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-004
Procedure number	Not applicable
Marketing Authorization Holder(s)	[redacted]
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 United Kingdom (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 Tumor Necrosis Factor Inhibitor (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
[redacted]	[redacted]

Marketing Authorization Holder(s)

[redacted]	[redacted]
[redacted]	[redacted]

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	adalimumab
AE	Adverse event
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
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
EC	Ethics committee
EMA	European Medicines agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETA	Etanercept
ESR	Erythrocyte sedimentation rate
EU	European Union
EU PAS	European union post-authorisation study
GPP	Guidelines for Good Pharmacoepidemiology Practices

[redacted]

Abbreviation	Definition
HAQ	Health assessment questionnaire
IEC	Institutional ethics committee
IFN	infliximab
IL	interleukin
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
JAKi	Janus Kinase inhibitor
Ltd	Limited
MI	Myocardial Infarction
NICE	National institute for Health and clinical excellence
PASS	Post-authorisation safety study
PhD	Doctor of Philosophy
mg	milligram
MI	Myocardial Infarction
MRes	Master of Research
RA	Rheumatoid Arthritis
REC	Research ethics committee
TB	Tuberculosis
TNFi	Tumour necrosis factor inhibitor
UK	United Kingdom
VAS	Visual analogue scale

[redacted]

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Country Coordinating Investigators

Not Applicable.

[redacted]

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: 22 July 2024

[redacted]

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 received marketing authorisation 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 RA at cohort entry will be used. This comparator cohort consists of RA patients initiating TNFi.

Variables: The study outcomes to be described 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 Disease activity score (DAS28), Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), tender and swollen join counts and pain Visual analogue scale (VAS). Patients analysed will be exposed to either tofacitinib, or anti-TNF therapy.

Data sources: BSRBR collects core baseline data, including patient demographics and disease characteristics, which are collected by the recruiting clinician using a standardised 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 available in July 2024.

[redacted]

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	July 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), the current study aims to address baseline characteristics, efficacy and continuation outcomes in a UK specific cohort of RA patients initiating tofacitinib. Similar studies have been conducted for other JAK's with marketing authorisation in the UK.[5] The data source for this study is taken from the ongoing 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.

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?

[redacted]

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 authorisation 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 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, Adalimumab [ADA], Etanercept [ETA] and Infliximab [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 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 RA who were treated with csDMARDs, and (ii) those with RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national

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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, generalisability 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 RA registered within 6 months of initiating tofacitinib. Recruitment to this cohort started at the time of UK marketing authorisation for tofacitinib (2017) and is ongoing.

2. TNFi-exposed patients with 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 30 November 2021, data collection from time of marketing authorisation 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.

[redacted]

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 9.2.1Inclusion 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.

Variable	Role	Data Source	Operational Definition
Sex (M/F)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient gender
Age, (years)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Calculated from 'Year of birth' to 'Drug start date'
Current height (kg) Current weight (cm)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patients current height in cm Patient's current weight in kg
Years of disease duration (years)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Years of disease duration

[redacted]

Variable	Role	Data Source	Operational Definition
Systolic pressure (mmHg) Diastolic pressure (mmHg)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Systolic blood pressure in mm Diastolic blood pressure in mm
Current/history of hypertension (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had high blood pressure
Current/history of angina (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had angina
Previous MI (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had MI
Previous stroke (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had stroke
Epilepsy (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had epilepsy
Asthma (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had asthma
COPD (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had COPD
Current/history of peptic ulcer (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had peptic ulcer
Current/history of liver disease (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had liver disease
Current/history of renal disease (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had renal disease
Current/history of TB (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had tuberculosis
Current/history of demyelination (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had demyelination
Current/history of diabetes (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had diabetes
Current/history of hyperthyroidism (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had hyperthyroidism

[redacted]

Variable	Role	Data Source	Operational Definition
Current/history of depression (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had depression
Current/history of cancer (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has ever had cancer
Current smoker (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient currently smokes
Ex-smoker (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient has previously smoked
Current/history of smoking (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient who previously smoked and/or currently smokes
Tender joint count (number)	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Tender joint count between 0 and 28
Swollen joint count (number)	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Swollen joint count between 0 and 28
ESR (mm/hr)	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	ESR count between 0 and 200
CRP (mg/dL)	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	CRP count to 2 decimal places
Patient global assessment VAS	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Global assessment score between 0-100mm
DAS28 total score	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	DAS28 total score between 0 and 10
HAQ score	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	HAQ overall mean score calculation
bDMARD naïve (Y/N)	Baseline Characteristic	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Patient's first exposure to a biologic agent
Patients continuing tofacitinib	Baseline Characteristic & Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Percentage of patients continuing on tofacitinib at any given timepoint from baseline

[redacted]

Variable	Role	Data Source	Operational Definition
Discontinuation due to inefficacy	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to inefficacy
Discontinuation due to remission	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to remission
Discontinuation due to adverse event	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to an adverse event
Discontinuation due to other	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to another reason
Discontinuation due to unknown	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued with an unknown reason
Discontinuation due to death	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to death
Discontinuation due to clinical indication, switch to biosimilar	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to clinical indication switch to a biosimilar
Discontinuation due to patient choice, switch to biosimilar	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued due to patient choice switch to a biosimilar
Discontinuation due to cost factors, switch to biosimilar	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued biosimilar switch for cost reasons
Discontinuation due to other, switch to biosimilar	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Of those patients who discontinued tofacitinib from baseline, the number (and percentage) of those who discontinued biosimilar switch for cost reasons
Time to discontinuation, days	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Time in days from drug start date to drug end date
Time to discontinuation due to inefficacy, days	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Time in days from drug start date to drug end date, when reason for discontinuation given is due to inefficacy
Time to discontinuation due to adverse event, days	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Time in days from drug start date to drug end date, when reason for discontinuation given is due to an adverse event
Time to discontinuation due to other, days	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Time in days from drug start date to drug end date, when reason for discontinuation given is due to other reason
Time to discontinuation due to death, days	Outcome	Raw dataset files received named 'BSRBR Xeljanz 30.11.21', 'BSRBR Anti-TNF 30.11.21' as collected per study A3921312.	Time in days from drug start date to drug end date, when reason for discontinuation given is due to death

[redacted]

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

[redacted]

- Past smoker
- Current/history of smoking
- Tender Joint count
- Swollen joint count
- ESR
- 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 authorisation in the UK for tofacitinib (2017), and from 2010 for TNFi).

[redacted]

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 RA who were treated with csDMARDs, and (ii) those with 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).

[redacted]

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.

9.7. Data Analysis

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 authorisation 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
Current/history of liver disease (Y/N)	Tofacitinib & TNFi cohorts	2&3	Number, % of cohort	Excluded	Baseline

[redacted]

Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
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 monthly intervals
bDMARD naïve (Y/N)	Tofacitinib & TNFi cohorts	2	Number, % of cohort	Excluded	Baseline

[redacted]

Measure	Analysis Set	Supports Protocol Objective Number	Planned descriptive analysis	Missing Data	Timepoint captured
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

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.

[redacted]

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. Documents or webpages that describe the overall governance of the data source and processes and procedures for data capture and management, data quality check and validation results (governing data access or utilisation for research purposes) can be found poses). https://www.bsrbr.org/hospitals/research-development/documents.

9.9. Limitations of the Research Methods

This study is designed to assess the safety of tofacitinib within the clinical practice setting utilising 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 analysable 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.

[redacted]

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymised 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 anonymised data from the existing BSRBR-RA, therefore patient consent is not applicable.

10.2. Patient Consent

As this study involves deidentified/anonymised 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 anonymised/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 anonymised 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)[10], EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[11].

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

[redacted]
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.

[redacted]

[redacted]

13. REFERENCES

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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.

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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.

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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.

10. Public Policy Committee ISoP. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016;25(1):2-10.

11. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 11). EMA/95098/2010.

14. LIST OF TABLES

[redacted]

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: 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)

[redacted]

[redacted]

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]	☒	☐	☐	Section 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? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section 8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, 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? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	Section 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? (eg, 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 structured data, no reporting of adverse events is required for this protocol.

[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.

[redacted]

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	Section 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)	☒	☐	☐	Section 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)	☐	☒	☐	
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☐	☒	☐	

[redacted]

Section 7: Bias	Yes	No	N/A	Section Number
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)	☒	☐	☐	Section 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?	☒	☐	☐	Section 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Section 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?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	Section 9.7
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

[redacted]

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)	☒	☐	☐	Section 9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 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?	☒	☐	☐	Section 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?	☒	☐	☐	Section 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?	☒	☐	☐	Section 5

Comments:

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

Comments:

Name of the main author of the protocol: [redacted]

[redacted]

Date: 17/July/2024

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

[redacted]