NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Real-world evaluation of effectiveness, persistence and usage patterns of tofacitinib in treatment of psoriatic arthritis in Australia.
Protocol number	A3921398
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Date	04 March 2021
EU Post Authorization Study (PAS) register number	EUPAS39635
Active substance	Tofacitinib citrate
Medicinal product	Xeljanz®
Research question and objectives	To understand the treatment patterns (lines of therapy, combination with other therapies or monotherapy), clinical effectiveness, patient reported outcomes and treatment persistence among Australian adult patients with psoriatic arthritis who are receiving tofacitinib.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical (classification)
bDMARD	biologic disease-Modifying antiheumatic drug
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease-modifying antirheumatic drug
CRP	C-reactive protein
DAPSA	Disease Activity in Psoriatic Arthritis
DAS28	Disease Activity Score in 28 joints
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
FACIT	Functional Assessment Of Chronic Illness Therapy
GPP	Good Pharmacoepidemiology Practices
HAQ-DI	health assessment questionnaire disease index
HCRU	Health Care Resource Utilisation
HL7	Health Level Seven
HREC	Human Research Ethics Committee
ICD-10	International Classification of Diseases 10
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IL17	interleukin 17 inhibitor
IRB	Institutional Review Board
ISPE	International Society for PharmacoEpidemiology
JAK	Janus Kinase
KM	Kaplan-Meier
LOINC	Logical Observation Identifiers Names and Codes
MP	multiprocessor
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
OPAL	Optimising Patient outcome in Australian rheumatoLogy
PBS	Pharmaceutical Benefits Scheme
PRO	patient reported outcome
PsA	psoriatic arthritis
QoL	quality of life
QUMI	Quality Use of Medicines Initiative
S4S	Software 4 Specialists (Clinical Software Developers For OPAL)
SAP	Statistical Analysis Plan
SDAI	Simple Disease Activity Index
TNFi	tumor necrosis factor inhibitor
tsDMARD	targeted synthetic disease modifying antirheumatic drug
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

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N/A.

4. ABSTRACT

Title: Real-world evaluation of effectiveness, persistence and usage patterns of tofacitinib in treatment of psoriatic arthritis in Australia.

Subtitle: Protocol V1.0 date: 04 March 2021

Rationale and Background: Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases and is a targeted synthetic Disease-Modifying Anti-Rheumatic Drug (tsDMARD) indicated for the treatment of psoriatic arthritis (PsA). It was approved for use in PsA in Australia in May 2018 and subsidised through the Pharmaceutical Benefits Scheme (PBS) from May 2019. Limited data exist to described the characteristics and outcomes of patients with PsA who receive tofacitinib in a real-world setting. This study aims to use the OPAL dataset to provide real-world evidence about the evidence regarding general treatment patterns, clinical effectiveness, treatment persistence and patient-reported outcomes (PROs) among PsA patients being treated with tofacitinib in the post-approval setting.

Research Question and Objectives: To understand the patterns of treatment (lines of therapy, and use as combination or monotherapy), clinical effectiveness, PROs and treatment persistence among Australian adult patients with PsA treated with tofacitinib. Similar data will also be collected for patients treated with biologic disease-modifying anti-rheumatic drugs (bDMARDs) to provide descriptive information about clinical management of PsA in real-world Australian clinical practice.

The primary objectives of the study are to describe tofacitinib treatment patterns among Australian adult patients with PsA, as defined by line of usage, dosing patterns, use as monotherapy or in combination with conventional DMARDs (cDMARDs) and reasons for discontinuation of tofacitinib; to assess the clinical effectiveness of tofacitinib, as defined by disease severity markers (Disease Activity Score-28 (DAS28), Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI)) Disease Activity Score Psoriatic Arthritis (DAPSA) and percent of patients reaching targeted treatment goals (remission or low disease activity), in Australia; and to assess PROs (Health Assessment Questionnaire – Disease Index (HAQ-DI), Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue, Health Care Resource Utilisation (HCRU)) and treatment persistence in Australian adult patients with PsA who are prescribed tofacitinib.

Secondary objectives are to describe bDMARD treatment patterns among Australian adult patients with PsA, as defined by line of usage, dosing patterns, use as monotherapy or in combination with cDMARDs and reasons for discontinuation of bDMARDs; to assess PROs (HAQ-DI, FACIT-Fatigue, HCRU) and treatment persistence in Australian adult patients with PsA who are prescribed bDMARDs.

Study Design: This is a retrospective non-interventional cohort study and will involve extracting real-world patient data from the Australian OPAL dataset.

Population: Data from adult patients (aged 18 years or older) with a diagnosis of PsA, who have received treatment with tofacitinib or a bDMARD and have at least 1 year of follow-up will be extracted from the OPAL database. In order to address the observational nature of the database, propensity score matching will be undertaken between the tofacitinib and bDMARD groups. Propensity score matching will be based on age, sex, DAS28 and baseline treatment combinations.

Variables: The following variables will be analysed: exposure (tofacitinib or bDMARDs), baseline characteristics (eg, baseline health, treatment history, clinical characteristics, PROs, treatment history) and outcomes (treatment patterns, clinical effectiveness and PROs).

Data Sources: All data for this study will be obtained from the OPAL dataset. The OPAL – Quality Use of Medicines Initiative is a point of care observational database.[1] Currently approximately 104 Australian rheumatologists and more than 192,000 patients with rheumatic disease are participating in the dataset. Data are captured into individual clinician's servers during routine clinical consultations, using the purpose-built worksheets in the Audit4 software.[4] Data de-identified for patient, clinic and clinician are exported from each of the OPAL member's local server to a central server for analysis.

Study Size: With 250 tofacitinib patients, proportions (eg, the proportion of first line users) can be estimated with a precision (ie, standard error of the estimate) of at worst ±7%. This is based on an estimated proportion of 50%.

Data Analysis: Descriptive summaries will be performed for each data cut and at the final analysis. No comparative analyses will be undertaken. Analyses will be repeated in the overall population and the propensity score matched population.

Milestones: Final study report completed by November 2022

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of Data Collection	15 April 2021
End of Data Collection	01 December 2021
Planned Date of EUPASS Registration	01 April 2021
Final Study Report	01 November 2022

7. RATIONALE AND BACKGROUND

Chronic inflammatory diseases such as psoriatic arthritis (PsA) have a significant negative impact on patients' health-related quality of life (QoL), and present a significant economic burden. Maximisation of health-related QoL is the primary goal of treatment. This is achieved through symptom and inflammation control, prevention of progressive structural damage, preservation or normalisation of function and social participation, and targeting remission.[1] Treatment of PsA usually involves a multifaceted approach that includes pharmacologic and non-pharmacologic strategies. Non-pharmacologic therapy may include physical, occupational, and psychological therapy, and surgery, while pharmacological therapy usually consists of various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, and synthetic or biologic disease modifying anti-rheumatic drugs (DMARDs).

Recently, a new oral targeted synthetic DMARD (tsDMARD), tofacitinib, has become available for the treatment of PsA. Tofacitinib is a potent, selective inhibitor of the Janus Kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. It was approved for use in Australia in May 2018 and included in the Pharmaceutical Benefits Scheme (PBS) (reimbursement) in May 2019. Limited data exist to describe the characteristics and outcomes of patients who receive tofacitinib in the real-world setting.

Patient reported outcomes (PROs) complement physician and laboratory measures in providing scientific evidence to support decisions regarding clinical therapy. The Outcome Measures in Rheumatology International consensus effort, the American College of Rheumatology, and the European League Against Rheumatism have recognized the importance of including a variety of PROs in randomized controlled trials.[2]

This study aims to use the Optimising Patient outcome in Australian rheumatoLogy (OPAL)[3] dataset to provide real-world evidence regarding general treatment patterns, clinical effectiveness, treatment persistence and PROs among PsA patients being treated with tofacitinib in the post-approval setting. Similar data will be collected for patients treated with bDMARDs to provide context in a real-world clinical practice setting. No formal comparisons between patients treated with tofacitinib and bDMARDs will be performed. An exploratory analysis and description of the most common reasons for discontinuation of treatments will be described. No safety analysis or analysis of adverse events will be performed.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

To understand the patterns of treatment (lines of therapy, and use as combination or monotherapy), clinical effectiveness, PROs and treatment persistence among Australian adult patients with PsA treated with tofacitinib. Similar data will also be collected for patients treated with bDMARDs to provide descriptive information about clinical management of PsA in real-world Australian clinical practice.

Objectives

8.1. Primary Objective

1. To describe tofacitinib, interleukin 17 inhibitor (IL17i), and tumor necrosis factor inhibitor (TNFi) treatment patterns among Australian adult patients with PsA, including:

    - Line of use (eg, first-line, second-line);
    - Mean dose;
    - Proportion of patients receiving monotherapy;
    - Proportion of patients using in combination with NSAIDs, corticosteroids and conventional disease-modifying antirheumatic drugs (cDMARDs);
    - Reasons for discontinuation.

Secondary objectives

1. To describe treatment persistence to IL17i, TNFi and tofacitinib in Australian patients with PsA.

2. To describe the clinical effectiveness of tofacitinib, IL17i, and TNFi, as defined by disease severity markers Disease Activity Score in 28 joints - erythrocyte sedimentation rate, (DAS28-ESR) Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), Disease Activity in Psoriatic Arthritis (DAPSA) [*if available*]) and the percentage of patients reaching targeted treatment goals (remission or low disease activity), in Australia.

3. To describe patient reported outcomes (HAQ-DI, FACIT-Fatigue, HCRU) in Australian adult patients with PsA between those prescribed tofacitinib and those prescribed other IL17i, or TNFi.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective, non-interventional secondardy structured data analysis cohort study of treatment patterns in patients prescribed IL17i, TNFi, or tofacitinib and will involve extracting real-world patient data from the Australian OPAL dataset.

Tofacitinib was listed on the Pharmaceutical Benefits Scheme (PBS) in May 2019. TNFi (adalimumab, certolizumab, etanercept, golimumab infliximab) and IL17i (secukinumab, ixekizumab) were already listed on the Pharmaceutical Benefits Scheme at this time.

Data will be extracted for the period 01 May 2019 until 30 September 2021 (sample window).

Included patients will be followed for a minimum of 1 year following their prescription of the index DMARD (IL17i, TNFi, or tofacitinib). Patients who discontinue their index DMARD will also be followed up for at least 1 year from time of the initial prescription of that treatment

All drugs will be prescribed, and all follow-up visits will be captured as part of normal medical practice. Patient therapeutic strategies will not be determined by the study protocol.

9.2. Setting

Data will be extracted from the Australian OPAL dataset database. The OPAL database collects information from individual clinicians' servers during routine clinical consultations, using purpose-built worksheets in Audit4 software. Pathology and imaging reports are electronically transferred from the pathology and radiology providers and are incorporated into the patient's medical record. This software serves as the patient's medical record.[3,4]

The activities of OPAL Rheumatology Ltd have received overarching ethics approval from the University of New South Wales Human Research Ethics Committee (HREC), based on a patient opt-out arrangement. De-identified data are exported from the clinician's server and encrypted. Aggregated data are sent to the OPAL Study Committee and study statistician. All research undertaken by OPAL requires the prospective approval of a properly constituted Australian HREC.

The database has collected information on more than 192,000 unique patients during 1 million clinical consultations from 43 rheumatologist clinics (and approximately 104 individual rheumatologists) around Australia. Of these 14,372 have a diagnosis of PsA.

Tofacitinib was reimbursed by the PBS in May 2019, so the start of the sample selection window will correspond to the time of approval.

The sample selection window is 01 May 2019 to 30 Sept 2020. Patients will be followed for a minimum one year, so the sampling window is 01 May 2019 to 30 Sept 2021.

It is estimated that approximately 460 patients taking tofacitinib, and more than 1500 patients taking bDMARDs will be enrolled in this study, however all relevant available data will be extracted. Data cuts used will be from September 2020 and September 2021.

This study includes adult patients (aged 18 years or older) with a diagnosis of PsA, who have received treatment with tofacitinib or a bDMARD and have at least 1 year of follow-up.

9.2.1. Inclusion Criteria

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

1. Diagnosed with PsA;
2. Aged 18 years but under 95 years of age on the index date (date of commencement of IL17i, TNFi, or tofacitinib);
3. Received at least 1 prescription for IL17i, TNFi, or tofacitinib; *and*
4. Have at least 1 year of follow-up since prescription of IL17i, TNFi, or tofacitinib.

9.2.2. Exclusion Criteria

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

1. Diagnosis with any autoimmune rheumatic disease except for PsA (eg, rheumatoid arthritis, ankylosing spondylitis).
2. Patients who have no visit data recorded within the sample window.
3. Patients who have missing start dates for IL17i, TNFi, or tofacitinib during the sample selection window.

9.2.3. Propensity Score Matching

Because of the observational nature of the data, analyses will be repeated both in the overall population, and also in a propensity score matched population. Propensity score matching increases the comparability of the observed baseline characteristics in patients treated with tofacitinib and other bDMARDs. The propensity score is the conditional probability of receiving treatment (eg, tofacitinib versus TNFi or tofacitinib versus IL17i), which is estimated using logistic regression.

The following independent covariates will be included as predictor variables in the propensity score:

- Patient age group at index:
  - 18-34;
  - 35-44;
  - 45-54;
  - 55-64;
  - 65-74;
  - >75.
- Sex:
  - Male;
  - Female.
- Disease severity:
  - DAS28-ESR, DAS28-CRP, CDAI, SDAI or DAPSA*.

    *Note choice of measure will depend on the availability of data.
- Select baseline treatments combinations (where baseline is the index date):
  - Methotrexate monotherapy;
  - Methotrexate + other conventional DMARD(s);
  - Conventional DMARD(S) other than methotrexate;
  - Neither methotrexate nor other conventional DMARD(s).

Tofacitinib users will be matched to TNFi users based on their propensity score from the above model. In the initial instance 2 matches for each tofacitinib patient will be sought. If 2 matches cannot be found for 80% of tofacitinib patients, the matching will be repeated seeking only 1 match for each tofacitinib patient. The use of a caliper width of 0.20 will be the starting point and this will be varied as needed.[5] For example, the caliper width can be increased if there are many tofacitinib patients for whom matches cannot be found.

A second propensity score matching model will match tofacitinib users to IL17i users based on their propensity score from the above model. In the initial instance 2 matches for each tofacitinib patient will be sought. If 2 matches cannot be found for 80% of tofacitinib patients, the matching will be repeated seeking only 1 match for each tofacitinib patient. The use of a caliper width of 0.20 will be the starting point and this will be varied as needed. For example, the caliper width can be increased if there are many tofacitinib patients for whom matches cannot be found.

In the comparative secondary outcomes, regression adjustment will be used to reduce bias due to residual differences (imbalance) in observed baseline covariates between the 2 treatment groups ie, those variables where a substantial difference still exists after matching will be included in any formal analyses as covariates.

Propensity score matching might not be feasible for reasons such as insufficient sample size within treatment groups of interest or insufficient overlap between groups (a loss of 50% or more tofacitinib patients ie, there are zero appropriate matches found for over 50% of tofacitinib patients during the propensity score matching exercise). In this case, only descriptive analyses will be conducted rather than matching analyses.

Further information on the propensity score matching method is available in the Statistical Analysis Plan (SAP).

9.3. Variables

Table 1. Baseline and Outcome Variables

Variable	Role	Data source(s)	Operational definition
Patient characteristics	Baseline characteristic	OPAL	Age, sex and presence of comorbidities
Clinical characteristics	Baseline characteristic,	OPAL	Disease duration, disease severity, disease activity (DAS28, SDAI, CDAI, Tender Joint Count (TJC), Swollen Joint Count (SJC) DAPSA, Disease Activity in PSoriatic Arthritis)
Patient reported outcomes	Baseline characteristic, outcome	OPAL	General health HAQ-DI, HCRU, Visual Analogue Scale VAS pain, FACIT-fatigue
Treatment history	Baseline characteristic, potential confounder	OPAL	Number, sequence and duration of previous DMARDs
Concomitant therapy	Baseline characteristic, potential confounder	OPAL	Type and dose of concomitant cDMARDs

Variable	Role	Data source(s)	Operational definition
Treatment duration	Outcome		Duration of treatment of the index b/tsDMARD
Clinical characteristics	Outcome,	OPAL	Disease activity (DAS28, SDAI, CDAI, Tender Joint Count (TJC), Swollen Joint Count (SJC) DAPSA, Disease Activity in PSoriatic Arthritis)

*Detailed definitions will be included in the SAP.

The following endpoints will be looked at within the different treatment groups to characterise the type of patients who are being prescribed IL17i, TNFi or tofacitinib, and to determine how these treatments are being used in clinical practice.

9.3.1. Patient Characteristics

Baseline demographic characteristics of each patient will be extracted based on data captured on the index date, or the closest measurements prior to the index date. These data will include:

- Age, sex and baseline comorbidities.

9.3.2. Clinical Characteristics

Clinical characteristics of each patient will include:

- Time since symptom onset at index.
- Disease severity:
  - DAS28-ESR/DAS28-CRP.
- Clinical Disease Activity Index (CDAI).
- Simple disease activity index (SDAI).
- DAPSA.
- Health assessment questionnaire for disease index (HAQ-DI).
- Health-care resource use questionnaire (HCRU).
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue).

- Baseline medication of interest:
  - NSAIDs/analgesics;
  - Corticosteroids;
  - Disease modifying antirheumatic drugs (DMARDs)
    The number, sequence, and duration of previous DMARDs will be collected. The duration of current bDMARD prior to the index date will be collected. The number and dose of concurrent conventional DMARDs will be collected.

9.3.3. Prior Biologic Treatment

Information on the number of prior bDMARD treatments will be summarised.

For the episodes of prior biologic treatment, the number falling into each of the following categories will be summarised:

- Combination – with methotrexate (MTX) and a cDMARD;
- Combination – with MTX only;
- Combination – with cDMARD only;
- Monotherapy.

9.3.4. Treatment Information

The number of patients prescribed the index DMARD in each treatment group will be summarised together with information on length of follow-up. The following summaries will be performed to assess the treatment patterns for patients in the IL17i, TNFi or tofacitinib treatment groups.

The dose of the index DMARD, line of use and concomitant cDMARD use will be summarised at the index date.

The number and percentage of subjects in each treatment group falling into the following categories at the index date will be summarized.

- Combination – with MTX and a cDMARD;
- Combination – with MTX only;
- Combination – with cDMARD only;
- Monotherapy.

The demographic characteristics of patients in each of the above categories will be examined.

Duration of treatment of the index DMARD will be summarised using Kaplan-Meier (KM) methods where subjects who have not discontinued will be censored at the last available assessment. In addition, for those receiving monotherapy treatment at the index date, duration of monotherapy treatment (ie, until either a switch to combination therapy with the same index DMARD or until discontinuation of the index DMARD) will be summarised. Similarly, for those receiving combination treatment at the index date, duration of combination treatment with the index DMARD will be summarised.

Reasons for discontinuation will also be summarised overall and by treatment combination (monotherapy, combination therapy).

9.3.5. Baseline

Baseline is defined as the measurements taken at the index date, or the closest measurement before the index date.

9.3.6. Outcomes

Analyses will be presented for the overall population and for the propensity score match population.

9.3.6.1. Treatment Patterns

Treatment patterns for patients in the 'tofacitinib group' the 'TNFi group' and 'IL17i group' will include line of usage, dose, frequency, and concomitant cDMARDs. Reasons for discontinuation will be collected.

9.3.6.2. Clinical Effectiveness

Clinical effectiveness will be assessed using disease severity (remission, low, moderate, high), DAS28, CDAI, SDAI and DAPSA scores. The proportion of patients reaching targeted treatment goals will be reported.

9.3.6.3. Patient Reported Outcomes

Patient reported outcomes include health assessment questionnaire for disease index (HAQ-DI) score, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) score, and Health Care Resource Utilisation (HCRU) score.

9.4. Data Sources

All data for this study will be obtained from the OPAL dataset. The OPAL – Quality Use of Medicines Initiative is a point of care observational dataset database.3,4 Currently approximately 104 Australian rheumatologists and more than 192,000 unique patients with rheumatic disease are participating in the dataset. Participating rheumatologists use an electronic patient management program that captures patient- and disease-specific details during routine physician-patient consultations.

OPAL members are based largely in private practice; however, this is representative of the Australian rheumatology community. OPAL members run clinics and collect data from both urban and rural clinics.

Data are captured into individual clinician's servers during routine clinical consultations, using the purpose-built worksheets in the Audit4 software.[3] Audit4 serves as the patient's medical record and produces the clinical correspondence for the consultation. Diagnoses are made by individual rheumatologists rather than being criteria based. Pathology and imaging reports are electronically transferred from the providers and incorporated into the patient's medical record.

The primary rheumatological condition and comorbidities are coded using the World Health Organisation (WHO) International Classification of Diseases 10 (ICD-10), and medications are mapped to the WHO Anatomical Therapeutic Chemical (classification) (ATC) System.

There are condition specific "clinical worksheets" such as a homunculus for tender and swollen joint counts, visual analogue scales and automatic calculation of DAS28 (Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP)).

Data de-identified for patient, clinic and clinician can be exported from each of the OPAL member's local server to a central server for analysis based on a predefined ethics-approved protocol.

9.5. Study Size

Sample size calculations are not applicable however, with 250 tofacitinib patients, proportions (eg, the proportion of first line users) can be estimated with a precision (ie, standard error of the estimate) of at worst ±7%. This is based on an estimated proportion of 50%. For lower or higher estimates the precision will be improved. (The size of the propensity score matched population of tofacitinib and IL17i /TNFi users may be smaller than this ie, if not all tofacitinib patients can be found matches).

9.6. Data Management

De-identified data will be extracted from the OPAL database. Permission to extract the data from the individual clinician's Audit4 software is obtained 3 to 4 weeks prior to the data extraction.

The sample selection window will be 01 May 2019 to 30 Sept 2020 and all patients with a bDMARD prescription during this time who meet the other eligibility criteria will be included in the extracted data set. A minimum of 1 year will occur for all sampled patients and therefore data up to 30 September 2021 will be included in the study.

The number and percentage of missing values will be included in the description of baseline characteristics. Missing values will not be imputed.

The patterns and predictors of missing variables will be explored for those covariates with 10% or greater missing values.

Analyses will be conducted using Stata Multiprocessor (MP) V14 (or higher), or equivalent statistical software.

9.7. Data Anlysis

Patients meeting the inclusion and exclusion criteria described in Section 9.2.1 and 9.2.3 will be categorised into 1 of 2 mutually exclusive drug cohorts, based on the type of DMARD received:

- Tofacitinib;
- All bDMARDs.

Baseline has been defined in Section 9.3.5.

All continuous variables will be summarised using n (non-missing sample size), mean, standard deviation, median, minimum and maximum. The frequency and percentages (based on the non-missing sample size) or observed levels will be reported for all categorical measures.

Descriptive summaries will be produced for each data cut, providing there is sufficient data available, and again at the final analysis.

All summaries are descriptive and there are no comparative analyses being undertaken, therefore, no adjustments for multiple data cuts and multiple endpoints are required.

Patients who discontinue their index treatment (tofacitinib, TNFi or IL17i) will continue to be followed for a period of 1 year.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Patient Demographics

Patient demographics will be summarised descriptively. Data will be presented overall, and by treatment group (tofacitinib and bDMARD).

9.7.2. Treatment Patterns

The number of patients prescribed tofacitinib or another bDMARD will be summarised. Information on length of follow-up (eg, mean, standard deviation, median, minimum, maximum) for the tofacitinib and bDMARD groups will be calculated. Persistence to treatment will be calculated.

Further information can be found in the SAP.

9.7.3. Clinical Effectiveness

The following summaries will be performed for patients in the tofacitinib treatment group. Summaries will be performed at baseline, 3, 9, 15, and 24 months with change from baseline also summarised at each post-baseline time point.

- DAS28;
- DAS28 change from baseline;
- CDAI;
- CDAI change from baseline;
- SDAI;
- SDAI change from baseline;
- DAPSA;
- DAPSA change from baseline;
- Number and % of patients reaching targeted treatment goals.

9.7.4. Patient Reported Outcomes

The following summaries will be performed for patients in the tofacitinib treatment group. Summaries will be performed at baseline, 3, 9, 15, and 24 months with change from baseline also summarised at each post-baseline time point.

- HAQ-DI;
- HAQ-DI change from baseline;
- FACIT-Fatigue;
- FACIT-Fatigue change from baseline;

- HCRU;
- HCRU change from baseline.

9.8. Quality Control

The Audit4 software is used at the point of care, and as such is a source document. Thus the data that is provided by clinicians to OPAL is a subset of the data that is a legal document which the clinician must ensure is accurate. For chemical pathology results, Audit4 has an internal quality control and only accepts values in the database where there is a corresponding Logical Observation Identifiers Names and Codes (LOINC) code and matching units as provided in the Health Level Seven (HL7) message from the pathology provider service. No additional formal quality control procedures are in place for OPAL.

9.9. Limitations of the Research Methods

This is a retrospective study based on data in the OPAL dataset. The analyses are therefore limited by the availability of data in this database. Data fields in the Audit4 software are not mandatory so there will likely be missing data points. The sample size, variables, and study duration have been selected to minimize the impact of this.

The Audit4 software records medically significant events, which are not necessarily serious adverse events (AE) and therefore it will be not be possible to stratify data into serious and non-serious AE.

The source data will be subject to logic checks in the software programming and individual clinicians are responsible for accurate data entry. Patient classifications are based solely on the physician's diagnosis.

The database only covers outpatient visits; inpatient visits are not included in this analysis.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Patient Withdrawal

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

The activities of OPAL Rheumatology Ltd have received overarching ethics approval from University of New South Wales Human Research Ethics. 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/IEC approvals must be forwarded to Pfizer.

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).[6]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This protocol will be registered on the Register of Post-Authorisation Studies. A clinical study report of all results will be generated, and results of this study will be submitted to a peer-reviewed journal. Authorship of the manuscript will be based on International Committee of Medical Journal Editors (ICMJE) criteria.

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 party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force [published correction appears in Ann Rheum Dis. 2018 Mar;77(3):472]. Ann Rheum Dis. 2018;77(1):3-17. doi:10.1136/annrheumdis-2017-211734.

2. Kirwan JR, Tugwell PS. Overview of the patient perspective at OMERACT 10--conceptualizing methods for developing patient-reported outcomes. J Rheumatol. 2011;38(8):1699-701.

3. Tymms K, Littlejohn G. OPAL: a clinician driven point of care observational data management consortium. Clin Exp Rheumatol. 2014;32(5 Suppl 85):S-150-2.

4. Roberts L, Arnold M, Bird P, Burnet S, De Jager J, Littlejohn G, et al. ARA-P39 Optimising patient outcomes in Australian rheumatology (OPAL) - a quality use of medicines initiative (QUMI) with >7000 rheumatoid arthritis (RA) patients. Internal medicine journal. 2011;41:9-38.

5. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.

6. Public Policy Committee - International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Annex 1 should be used to list stand-alone documents not included in the protocol, eg, contact details of responsible parties and all investigators if applicable.

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

For PASS protocols submitted in the EU, a copy of the ENCePP Checklist for Study protocols (available at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml) should be completed and signed by the main author of the study protocol, and included in Annex 2.

For all other NI studies (ie, PASS protocols not submitted in the EU and non-PASS protocols), this annex is not required.

ANNEX 3. ADDITIONAL INFORMATION

Additional annexes may be included if necessary. If not needed, enter “Not applicable”.

Not Appicable.

Document Approval Record

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