NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

Study information

Title	An evaluation of non-melanoma skin cancer and melanoma skin cancer rates among patients treated for moderately to severely active rheumatoid arthritis with Xeljanz(REGISTERED) (tofacitinib citrate): A retrospective non-interventional database study of observational data embedded within Optimising Patient outcome in Australian RheumatoLogy - Quality Use of Medicines Initiative (OPAL-QUMI)
Protocol number	A3921291
Protocol version identifier	2.0
Date of last version of protocol	06 May 2019
EU Post-Authorisation Study (PAS) register number	EUPAS18431
Active substance	Tofacitinib citrate
Medicinal product	Xeljanz (REGISTERED)
Research question and objectives	To provide real-world evidence about the rates of non-melanoma skin cancer and melanoma skin cancer in adult patients with moderately to severely active rheumatoid arthritis, as measured by Disease Activity Score-28 at baseline, who are treated with tofacitinib.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
ATC	Anatomical Therapeutic Chemical
bDMARDs	Biologic Disease Modifying Anti-Rheumatic Drugs
CDAI	Clinical Disease Activity Index
cDMARDs	Conventional Disease Modifying Anti-Rheumatic Drugs
CRF	Case report forms
DCT	Data collection tool
CRP	C-Reactive Protein
DAS28	Disease Activity Score-28
DMARDs	Disease Modifying Anti-Rheumatic Drugs
ESR	Erythrocyte Sedimentation Rate
EU	European Union
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
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JAK	Janus Kinase
MSC	Melanoma Skin Cancer
MP	Multiprocessor
LOINC	Logical Observation Identifiers Names and Codes
NIS	Non-Interventional Study
NMSC	Non-Melanoma Skin Cancer
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPAL	Optimising Patient Outcome in Australian Rheumatology
PASS	Post-Authorisation Safety Study

Abbreviation	Definition
PBS	Pharmaceutical Benefits Scheme
QUMI	Quality Use of Medicines Initiative
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan
SDAI	Simple Disease Activity Index
SJC	Swollen Joint Count
TJC	Tender Joint Count
tsDMARDs	Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs
VAS	Visual Analogue Scale
WHO	World Health Organisation

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Title: An evaluation of non-melanoma skin cancer (NMSC) and melanoma skin cancer (MSC) rates among patients treated for moderately to severely active rheumatoid arthritis with Xeljanz(REGISTERED) (tofacitinib citrate): A retrospective non-interventional database study of observational data embedded within Optimising Patient outcome in Australian RheumatoLogy - Quality Use of Medicines Initiative (OPAL-QUMI).

Version: 2.0 dated 06 May 2019

Main Author: Associate Professor Paul Bird, Director, Combined Rheumatology Practice Director, Optimus Clinical Research, Suite 4, Level 1, 19 Kensington Street, Kogarah NSW 2217.

Rationale and Background: 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 February 2015 and reimbursed by the Pharmaceutical Benefits Scheme in Australia in October 2015. Being the first oral JAK inhibitor and the only targeted synthetic Disease Modifying Antirheumatic Drugs (tsDMARD) for the treatment of moderate to severe rheumatoid arthritis (RA), there is a need to gather emerging real-world long-term safety data. These data will help to further contextualise and expand knowledge about the benefit to risk profile of tofacitinib in RA. This study aims to use the OPAL registry to provide real-world evidence about the rates of NMSC and MSC in adult patients with RA who are treated with tofacitinib. This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

Research Question and Objectives: To determine rates of NMSC and MSC among Australian patients with RA treated with tofacitinib or biologic disease modifying anti-rheumatic drugs (bDMARDs). Data will be stratified by patient demographics and clinical characteristics. The primary objectives for this study are to determine the rate of NMSC and MSC among patients treated for moderately to severely active RA, as measured by Disease Activity Score-28 (DAS28) at baseline, with tofacitinib. The secondary objectives are to determine: the rate of NMSC and MSC among patients treated for moderately to severely active RA, as measured by DAS28 at baseline, with bDMARDs.

Study Design: This is a retrospective, non-interventional cohort study of rates of NMSC and MSC in patients treated with tofacitinib or bDMARDs, and will involve extracting real-world patient data from the Australian OPAL registry. Data will be extracted for the period 01 February 2015 until 01 September 2018. All drugs are prescribed and all follow-up visits are captured as part of normal medical practice. Patient therapeutic strategies are not be determined by the study protocol (i.e therapeutic strategies are determined by the treating physician during routine clinical consultation).

Population: This study includes adult patients (aged 18 years or older) with a diagnosis of RA, who have received treatment with tofacitinib or a bDMARD and have at least 1 year of follow-up. Patients with any autoimmune rheumatic disease or inflammatory bowel

conditions except for RA (eg, psoriatic arthritis, ankylosing spondylitis, psoriasis Crohn's disease or ulcerative colitis) are excluded.

Variables: The following variables will be analysed: exposure (tofacitinib or bDMARDs), baseline characteristics (eg, demographics, medical history, clinical characteristics, patient reported outcomes, treatment history) and outcomes (incidence rate and incidence density rate of NMSC and MSC).

Data Sources: All data for this study will be obtained from the OPAL registry. The OPAL – Quality Use of Medicines Initiative is a point of care observational registry database.[1] Currently approximately 80 Australian rheumatologists and more than 35,000 patients with rheumatic disease are participating in the registry. Data are captured into individual clinician's servers during routine clinical consultations, using the purpose-built worksheets in the Audit4 software.[2] 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: 500 patients administered tofacitinib and 2,500 patients administered bDMARDs.

Data Analysis: Analysis will be descriptive. Incidence density rates for NMSC and MSC will be calculated for 'tofacitinib' and 'bDMARD' groups.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	16 January 2019	Substantial	Section 10	Changed safety language because the protocol has been amended to include human review of unstructured data	The histopathology data for each NMSC/MSC case, where available will be reviewed manually, which will involve protocol-required human review of unstructured data (e.g. patient's medical record
1	16 January 2019	Administrative	Section 8.3	Changed definition of Index DMARD from "If the patient has been prescribed more than one of the drugs of interest (ie, tofacitinib or bDMARD), the index DMARD will be considered tofacitinib for those ever receiving tofacitinib, or the first prescription of a bDMARD ('bDMARD group') if the patient has never received tofacitinib." to "If the patient has been prescribed more than one of the drugs of interest (ie, tofacitinib or bDMARD), the index DMARD will be considered the first prescription of tofacitinib or a new bDMARD within the sample selection window."	To avoid imbalances between both groups.

5. MILESTONES

Milestone	Planned Date
Protocol approval	29 March 2017
Human Research Ethics Committee (HREC) submission	30 March 2017
Registration in the EU PAS register	31 March 2017
Start of data collection	31 March 2017
Interim report 1: 1st data cut*	01 March 2017
Interim report 2: 2nd data cut*	01 September 2017
Interim report 3: 3rd data cut*	01 March 2018
Interim Report 4: 4th data cut*	01 September 2018
End of data collection: 5th data cut*	01 September 2019
Final study report	01 July 2020

**Dates are subject to change, depending on the number of tofacitinib and bDMARDs patients enrolled and the duration of follow-up at the time to ensure that the agreed number of patients have been enrolled and the agreed follow-up data collected at the time of each report. Data reports will be available within four weeks of data cut, except for the first data cut, which will be available within eight weeks of the data cut.*

6. RATIONALE AND BACKGROUND

Patients with rheumatoid arthritis (RA) undergo treatment with 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. 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 February 2015 and reimbursed by the Pharmaceutical Benefits Scheme in Australia in October 2015. Being the first oral JAK inhibitor for the treatment of moderate to severe RA, there is a need to gather emerging real-world long-term safety data. These data will help to further contextualise and expand knowledge about the benefit to risk profile of tofacitinib in RA.

Compared to the general population, patients with RA are at increased risk of melanoma.[3] The relationship between biologic DMARDs (bDMARDs) and risk of melanoma (MSC) or non-melanoma skin cancer (NMSC) have not been definitively established, with some reports suggesting increased rates of MSC and NMSC.[3,4] Other Australian studies have not

found an increase of malignancy with exposure to bDMARDs,[4] however, conventional synthetic DMARDs do appear to be associated with an increase in NMSC.[5]

This study aims to use the Optimising Patient outcome in Australian rheumatoLogy (OPAL) registry to provide real-world evidence about the rates of NMSC and MSC in adult patients with RA who are treated with tofacitinib. The analyses will be based on patients with RA who are administered tofacitinib. Similar data will be collected for patients treated with bDMARDs to provide context about rates and types of NMSC and MSC in a real-world clinical practice setting. No formal comparisons between rates of NMSC and MSC in patients treated with tofacitinib and bDMARDs will be performed.

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

7. RESEARCH QUESTION AND OBJECTIVES

Research question

To determine rates of NMSC and MSC among Australian patients with moderately to severely active RA treated with tofacitinib or bDMARDs. Data will be stratified by patient demographics and clinical characteristics.

Objectives

The primary objectives for this study are:

1. To determine the rate of NMSC among patients treated for moderately to severely active RA, as measured by DAS28 at baseline, with tofacitinib.

2. To determine the rate of MSC among patients treated for moderately to severely active RA, as measured by DAS28 at baseline, with tofacitinib.

Secondary objectives are to determine:

1. The rate of NMSC among patients treated for moderately to severely active RA, as measured by DAS28 at baseline, with bDMARDs.

2. The rate of MSC among patients treated for moderately to severely active RA, as measured by DAS28 at baseline, with bDMARDs.

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective, non-interventional cohort study of rates of NMSC and MSC in patients treated with tofacitinib or bDMARDs, and will involve extracting real-world patient data from the Australian OPAL registry. Data will be extracted for the period 01 February 2015 until 01 September 2018.

All drugs are prescribed and all follow-up visits are captured as part of normal medical practice. Patient therapeutic strategies are not be determined by the study protocol (i.e. therapeutic strategies are determined by the treating physician during routine clinical consultation).

8.2. Setting

Data will be extracted from the Australian OPAL registry 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.[2]

The activities of OPAL Rheumatology Ltd have received overarching ethics approval from the University of New South Wales Human Research Ethics Committee, 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 Human Research Ethics Committee.

The database has collected information on more than 32,000 patients from 42 rheumatologist clinics (and approximately 80 individual rheumatologists) around Australia. Of these 23,000 have a diagnosis of RA.

Tofacitinib was approved by the Therapeutic Goods Administration in February 2015, so the start of the sample selection window will correspond to the time of approval.

The sample selection window is 01 February 2015 to 01 September 2018. Patients will be followed for a minimum one year, so the sampling window is 01 February 2015 to 01 September 2018.

It is estimated that approximately 500 patients taking tofacitinib, and more than 2,500 patients taking bDMARDs will be enrolled in this study, however all relevant available data will be extracted. Data cuts occur in March 2017, September 2017, March 2018, September 2018 and September 2019

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

8.2.1. Inclusion Criteria

Patients must meet <u>all</u> the following inclusion criteria to be eligible for inclusion in the study:

1. Diagnosed with RA, based on DAS28;

2. At least 18 years of age on the date of commencement of tofacitinib or a bDMARD;

3. Received at least one prescription for tofacitinib or a bDMARD; and

4. Have at least 1 year of follow-up since prescription of the index DMARD (tofacitinib or a bDMARD).

8.2.2. Exclusion Criteria

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

1. Diagnosis with any autoimmune rheumatic disease or inflammatory bowel disease except for RA (eg, psoriatic arthritis, ankylosing spondylitis, psoriasis Crohn's disease or ulcerative colitis).

8.3. Variables

The primary exposure of interest is an initial prescription for tofacitinib or a bDMARD identified during the sample selection window. The date of the first prescription after the start of the sample selection window will serve as the study index date and the beginning of the post-index period.

Index DMARD: the agent of interest identified during the sample selection window (01 February 2015 to 01 September 2017) using Anatomical Therapeutic Chemical (ATC) codes. If the patient has been prescribed more than one of the drugs of interest (ie, tofacitinib or bDMARD), the index DMARD will be considered the first prescription of tofacitinib or a newbDMARD within the sample selection window

8.3.1. Exposure

Prior to the full assessment of the outcomes related to the exposure, the prescription data will be evaluated for missing data (eg, strength, or quantity) and to identify implausible values (eg, usually high quantity, or dosage). Implausible values will be adjudicated by two experienced rheumatologists who are members of the OPAL board and independent of the Sponsor. The recommended dosing schedule for tofacitinib and bDMARD is shown in Table 1.

Table 1. Recommended Dosage for DMARDs

Agent	Recommended Dose*
Abatacept	Weight based dosing (500 mg if <60 kg; 750 mg if 60 to 100 kg; 1 g if >100 kg) administered as intravenous infusion over 30 minutes.
Adalimumab	40 mg sc fortnightly, or 40 mg weekly in patients not taking methotrexate.
Anakinra	100 mg per day administered as a subcutaneous injection.
Certolizumab	400 mg (as 2 injections of 200 mg each on one day) at Weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks. Alternatively, a maintenance dose of 400 mg every 4 weeks may be given.
Etanercept	50 mg weekly given as a subcutaneous injection, either once weekly as a single injection or twice weekly as two separate 25 mg injections given 3 to 4 days apart.
Golimumab	50 mg given as a subcutaneous injection once a month, on the same date each month.
Infliximab	Patients not previously treated with infliximab: initially 3 mg/kg to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion then 8 weeks thereafter. Doses may be adjusted in increments of 1.5 mg/kg up to a maximum of 7.5 mg/kg.
Rituximab	1,000 mg by intravenous infusion followed by 1,000 mg by intravenous infusion two weeks later.
Tocilizumab	8 mg/kg every four weeks as an intravenous infusion, with doses not exceeding 800 mg, or 162 mg weekly subcutaneously.
Tofacitinib	5 mg twice daily orally.

**Recommended dose based on Australian prescribing information.*

8.3.2. Baseline

Baseline characteristics of interest are listed in Table 2. Baseline is defined as the measurements taken at the index date, or the closest measurement before the index date.

Table 2. Baseline Characteristics

Variable	Role	Data source(s)	Operational definition
Patient demography	Baseline characteristic	OPAL	Age, sex
History and classification of malignancy	Baseline characteristic, potential confounder	OPAL	Prior history of malignant cancers, including clinical classification and treatment outcomes/ interventions.
Baseline Health	Baseline characteristic	OPAL	Presence of comorbidities
Clinical characteristics	Baseline characteristic	OPAL	Disease duration, disease severity, Disease Activity Score (DAS), Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Tender Joint Count (TJC), Swollen Joint Count (SJC)
Health assessment	Baseline characteristic	OPAL	General health (Health Assessment Questionnaire – Disease Index (HAQ-DI), Visual Analogue Scale (VAS)
Patient reported outcomes and treatments	Baseline characteristic	OPAL	Number, sequence and duration of previous DMARDs (HAQ-DI, Health Care Resource Utilisation (HCRU), Functional Assessment Of Chronic Illness Therapy (FACIT)-fatigue)
Treatment history	Baseline characteristic, potential confounder	OPAL	Dose and prior duration of treatment with DMARDs
Concomitant therapy	Baseline characteristic, potential confounder	OPAL	Type and dose of concomitant cDMARDs

8.3.3. Outcome

The incidence rate of NMSC and MSC will be calculated as follows:

$$Incidence\ Rate = \frac{Number\ of\ new\ cases\ of\ NMSC\ or\ MSC}{Number\ of\ patients\ treated\ with\ tofacitinib\ or\ bDMARD}$$

The incidence density rate will be calculated as:

$$Incidence\ Density\ Rate = \frac{Number\ of\ new\ cases\ of\ NMSC\ or\ MSC}{\sum person\ time\ at\ risk}$$

Events will be calculated per 100 patient-years of observation.

8.4. Data Sources

All data for this study will be obtained from the OPAL registry. The OPAL – Quality Use of Medicines Initiative is a point of care observational registry database.[1] Currently approximately 80 Australian rheumatologists and more than 35,000 patients with rheumatic disease are participating in the registry. 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.[2] 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 (ATC) Classification 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.

8.5. Study Size

The estimated NMSC and MSC density rate in patients with bDMARDs and the estimated follow-up exposure in patient-years to tofacitinib required to detect an assumed increased risk relative to bDMARDs with 90% power is shown in Table 3:

Table 3. Patient Years' Exposure to Tofacitinib Required for the Lower Bound of the 95% Confidence Interval to Exceed Background Rate in External bDMARD Comparator Populations Assuming an Increase in Observed Rate of 1.2x, 1.5x, or 2.0x[6]

Event	IR reported for external bDMARD comparator population per 100 patient-years	Follow-up exposure (patient-years) to tofacitinib required to detect an assumed increased risk relative to bDMARDs with 90% power		
		1.2	1.5	2.0
Malignancy (including MSC)	0.79 to 1.14	25,734 to 38,165	4,743 to 6,872	1,413 to 2,004
NMSC	0.21 to 1.34	22,366 to 137,762	3,933 to 25,444	1,146 to 7,263

Given these numbers, and on the basis that 500 patients on tofacitinib and 2,500 patients on bDMARDs are planned to be recruited, the study is not sufficiently powered to make comparisons in rates of MSC or NMSC between tofacitinib and bDMARDs. Therefore, the primary and secondary incident rate analysis will be descriptive only and no comparisons between bDMARD and tofacitinib are planned.

8.6. 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 three to four weeks prior to the data extraction.

The sample selection window will be 01 February 2015 to 01 September 2018 and all patients with a bDMARD/tofacitinib prescription during this time who meet the other eligibility criteria will be included in the extracted data set. A minimum of one year follow-up will occur for all sampled patients and therefore data up to 01 September 2019 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.

8.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF/DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

For purposes of validating patient reported events, OPAL will develop a CRF/DCT with patient identification number only, so that patient identifiable information will not be collected by Pfizer. OPAL will maintain a separate histopathology reporting form with patient identifiable information that is not the property of Pfizer.

A CRF/DCT is required and should be completed for each included patient. The completed original CRFs/DCT] are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs/DCTs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The *investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs*/DCTs *and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs*/DCTs *must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs*/DCTs *are true. Any corrections to*

entries made in the CRFs/DCTs *or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.*

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs/DCTs *must match those charts*.

8.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, OPAL agrees to keep all study-related records, e.g. CRFs/DCTs The records should be retained by OPAL according to local regulations or as specified in the vendor contract, research agreement, whichever is longer. OPAL must ensure that the records continue to be stored securely for so long as they are retained.

If OPAL becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless OPAL and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

OPAL must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Data Analysis

Patients selected according to the inclusion and exclusion criteria described above will be categorised into one of two mutually exclusive drug cohorts, based on the first DMARD prescribed during the sample selection window:

- Tofacitinib
- All bDMARDs

Baseline has been defined in Section 8.3.2.

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 are 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 or bDMARD) will continue to be followed for a period of 1 year.

All cases of NMSC and MSC will be confirmed by a single healthcare professional who will review the histopathology data retrieved from the patient's medical records, if available.

8.7.1. Patient Demographics

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

8.7.2. Primary Objective

The primary objective is to determine the rate of NMSC and MSC among patients treated for moderately to severely active RA, as measured by DAS28 at baseline, with tofacitinib. The incidence rate and incidence density rate of NMSC and MSC will be calculated as per Section 8.3.3.

Histopathology, staging and treatment (eg, excision or cryotherapy) will be collected and confirmed for all skin cases, if available. If it is not possible to confirm the categorisation (NMSC vs MSC), the data will be stratified as "*case reported by the patient but not confirmed by histopathology data*" or "*case confirmed by histopathology data*".

Incidence rates and incidence density rates of NMSC and MSC will be calculated overall. In addition, a Poisson regression model will be built that includes the following covariates:

- Disease duration;
- Disease activity (as measured by DAS28);
- Duration of treatment;
- Treatment (tofacitinib vs bDMARD).

Exposure time will be included in the model.

8.7.3. Secondary Objective

Secondary objectives on the incidence rate and incidence density rate will be analysed as per the primary objective (see Section 8.7.2).

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.

8.8. Quality Control

The Audit4 software is used at the point of care, and as such is a source document. Thus the data that are 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.

8.9. Strengths and Limitations of the Research Methods

8.9.1. Strengths

This is a retrospective cohort study of real-world evidence, thus the incidence of NMSC and MSC in a real-world setting can be estimated.

8.9.2. Limitations

This is a retrospective study based on data in the OPAL registry. 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 and therefore it will be not be possible to stratify data into serious and non-serious adverse events.

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.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at Suite 4, Level 1, 19 Kensington Street, Kogarah NSW 2217 in encrypted electronic and form and will be password protected to ensure that only authorized study staff have access. OPAL will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, OPAL shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law."

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract and applicable privacy laws.

9.2. Patient consent

9.3.

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

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.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).[7]

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual.

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of

medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the histopathology verification form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members will complete the following Pfizer training requirements: "YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)". These training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.
Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This protocol is 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.

12. COMMUNICATION OF ISSUES

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 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.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

13. REFERENCES

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2. 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.

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4. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007;56(9):2886-95.

5. Lange E, Blizzard L, Venn A, Francis H, Jones G. Disease-modifying anti-rheumatic drugs and non-melanoma skin cancer in inflammatory arthritis patients: a retrospective cohort study. Rheumatology (Oxford). 2016;55(9):1594-600.

6. Curtis JR, Zhang R, Krishnaswami S, Anisfeld A, Chen Y, Strengholt S, et al. Use of a risk characterisation approach to contextualise the safety profile of new rheumatoid arthritis treatments: a case study using tofacitinib. Clinical rheumatology. 2016.

7. Public Policy Committee - International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016;25(1):2-10.

14. LIST OF TABLES

Please refer to the *Statistical Analysis Plan.*

15. LIST OF FIGURES

Please refer to the *Statistical Analysis Plan.*

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.