NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A Longitudinal, Retrospective, Multi-centre Observational Study to Evaluate Effectiveness, Persistence, Treatment Patterns and Safety of Australian Patients Receiving Early Access to Tofacitinib
Protocol number	A3921405
Protocol version identifier	2.0
Date	23 September 2021
EU Post Authorization Study (PAS) register number	EUPAS41439
Active substance	ATC code: L04AA29 tofacitinib-citrate
Medicinal product	Xeljanz®
Research question and objectives	**Research question and objectives**: Examine the disease characteristics and outcomes in ulcerative colitis patients granted access to tofacitinib in Australia using deidentified patient information.
Author	Redacted

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
5-ASA	5- Aminosalicylic Acid
CI	confidence Interval
CRF	Case Report Form
CRP	C-reactive protein
CSA	Clinical study agreement
CV	Cardiovascular
DVT	Deep Vein Thrombosis
ESR	Erythrocyte Sedimentation Rate
FU	follow-up
GPP	Guidelines For Good Pharmacoepidemiology Practices
HCV Ab	Hepatitis C Virus Antibody
HDL	High Density Lipoprotein
HZ	Herpes Zoster
HREC	Human Research Ethics Committee
IBD	Inflammatory Bowel Disease
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society For Pharmacoepidemiology

Abbreviation	Definition
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MES	Most Recent Endoscopic Severity
MACE	Major Adverse Cardiovascular Event
NHMRC	National Health and Medical Research Council
NIS	Non-Interventional Study
NMSC	Non-Melanoma Skin Cancer
NRI	Non-Responder Imputation
NSTEMI	Non-ST-Elevation Myocardial Infarction
PASS	Post-Authorization Safety Study
PBS	Pharmaceutical Benefit Scheme
PE	Pulmonary Embolism
PI	Package Insert
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STEMI	ST-Elevation Myocardial Infarction
TGA	Therapeutic Goods Administration
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
UK	United Kingdom
USA	United States of America
VTE	Venous thromboembolism

Abbreviation	Definition
YRR	Your Reporting Responsibility

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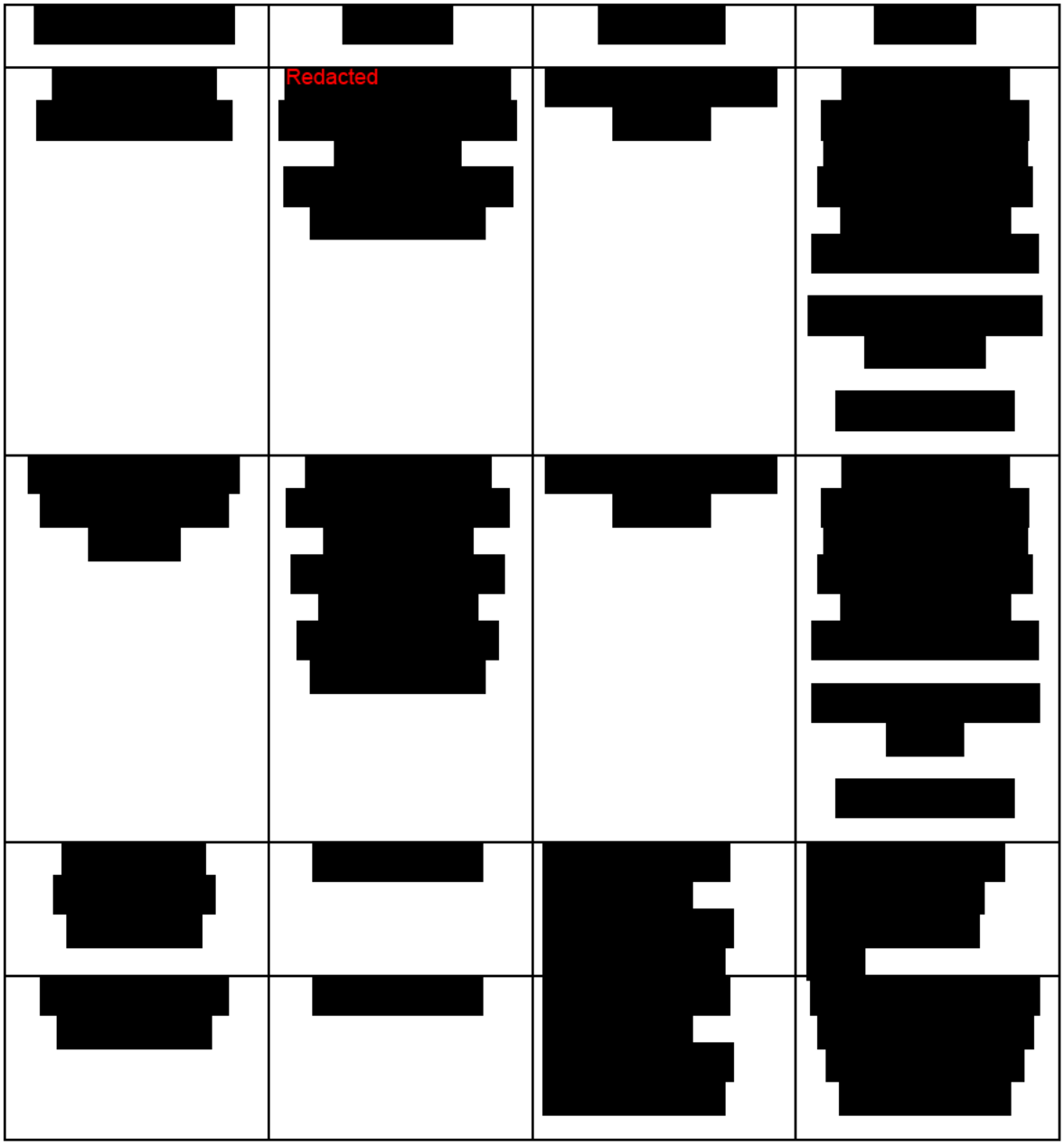

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4. ABSTRACT

See ANNEX 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	23 September 2021	Title Page and Section 3 Responsible Parties	Redacted	Administrative
		Section 3 Responsible Parties	Redacted	Administrative
		Section 3 Responsible Parties	Redacted	Administrative
		Annex 1. Stand Alone Documents	Change in Annex 1 (abstract) version date.	Administrative
		Annex 3. Additional Information	List of proposed sites added in Annex	Administrative

6. MILESTONES

Milestone	Planned date
Start of data collection	22 October 2021
End of data collection	08 July 2022
Registration in the EU PAS register	30 September 2021
Final study report	19 August 2022

7. RATIONALE AND BACKGROUND

Tofacitinib was approved for the treatment of UC (Ulcerative Colitis) by the Australian Regulatory Agency (Therapeutic Goods Administration or TGA) in February 2019. It does not yet have public reimbursement by the Pharmaceutical benefits scheme (PBS), but has been supplied on a case-by-case basis by Pfizer for physicians requesting it for their patients. Currently, there are more than 300 UC patients who have been treated with tofacitinib since TGA approval. The vast majority of treated patients have failed previous biologic therapy. There has been limited data presented on the response of patients to tofacitinib after previously failing anti-TNF (Tumor Necrosis Factor) and anti-integrin therapies. This data may be particularly germane to the Australian prescribing landscape where the positioning of tofacitinib in UC patients with respect to other treatments is not yet established for reimbursement purposes.

Tofacitinib has been shown effective in moderate to severe UC in three phase 3 randomized, double-blind, placebo-controlled studies, two studies assessing induction (OCTAVE induction 1 and 2) and one for maintenance therapy (OCTAVE Sustain).[1] The real-world data on the effectiveness and safety of tofacitinib is limited. A pubmed database search done on 08 June 2021 with search items 'Tofacitinib', 'UC' and 'Real-world' or 'Observational' identified only 7 full text articles. These studies were observational, multicentre or single centre, retrospective or prospective studies looking at effectiveness as well as safety in real world. The outcomes studied are summarized in Table 1. A meta-analysis published in 2021 which searched MEDLINE, EMBASE and conference proceedings identified 17 studies with 1162 patients including 6 full text articles and also 11 conference proceedings.[2] These studies identified concluded that tofacitinib is safe and effective for treatment of UC specifically refractive UC patients and its benefit-risk profile is consistent with the clinical trial evidence.[1-9]

It was important to note that there is no data published on the real-world effectiveness and safety of tofacitinib in Australian UC patients.[2-9] This non-interventional study will address this data gap as well as add to the real-world evidence already published.

Table 1. Published Real World Studies Evaluating Tofacitinib in UC[2-9]

Author	Year	Country	Location	Study design	Number of patients	FU (follow-up) (weeks)	Assessed Outcomes						
							Week 8	Week 12-16	Month 6	Month 12	Colectomy	Prolonged induction	Safety
Biemans[3]	2019	Netherlands	Multicentre	Prospective	123	24		1-4	1-3		Yes		Yes
Honap[4]	2020	UK (United Kingdom)	Multicentre	Retrospective	134	26	1-3	1-3	1-3		Yes	Yes	Yes
Lair-Mehiri[5]	2019	France	Multicentre	Retrospective	38	41		3, 4	3, 4	3, 4	Yes		Yes
Shimizu[6]	2020	Japan	Unicentre	Retrospective	30	23	1, 2		1, 2	1, 2			Yes
Weisshof[7]	2019	USA (United States of America)	Unicentre	Retrospective	80	42	1-4		1-3	1, 3	Yes	Yes	Yes
Chaparro[8]	2020	Spain	Multicentre	Retrospective	113	44	1, 2	1, 2				Yes	Yes
Deepak[9]	2020	USA	Multicentre	Retrospective	260	52					Yes		Yes

Clinical outcomes assessed at week 8, week 12-16, month 6, and month 12. Assessed outcomes: 1) Clinical response, 2) Clinical remission, 3) Corticosteroid-free clinical remission, 4) Endoscopic improvement.

This study proposes to examine the disease characteristics and outcomes in UC patients granted access to tofacitinib in Australia using deidentified patient information to inform practice.

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

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question:

Examine the disease characteristics and outcomes in ulcerative colitis patients granted access to tofacitinib in Australia using deidentified patient information. There are more than 300 ulcerative colitis patients who have been treated with tofacitinib since its TGA approval. The vast majority of patients who have been granted compassionate access have failed one or more previous biologic therapies. There has been limited data presented on the response of patients to tofacitinib after previously failing anti-TNF and anti-integrin therapy such as vedolizumab.

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8.2. Objectives:

The primary outcome for this study is clinical response at the end of induction. Since this is a real-world study, standard induction will be considered response at week 8-12, depending on when patients were assessed by their treating physician. Extended induction response will be considered at week 16, as per standard of care. Clinical response is defined as a decrease in the partial Mayo score by 2 or an overall partial Mayo score <2. The secondary endpoints include clinical remission at week 8 and week 16 (partial Mayo score <2 with no individual sub score greater than 1), resolution of rectal bleeding, endoscopic healing in those who had endoscopy, need for extended induction (16 weeks), cessation of steroids in those on steroids at commencement of tofacitinib, steroid free clinical remission at the end of induction (week 8 or 12) and week 16, improvement in calprotectin for patients with baseline and follow-up results and other biomarkers compared to the baseline characteristics where available. Reasons for discontinuation and to describe the safety profile of tofacitinib during treatment period with respect to AEs (adverse events), SAEs (serious adverse event), discontinuation due to AEs, and adverse events of special interest i.e Hospitalization, Infectious complications, Serious infections, Opportunistic Infections; Incidence of Herpes Zoster and extent (one or multiple dermatomes, ocular, systemic disease), MACE (Major Adverse Cardiovascular Event), DVT (Deep Vein Thrombosis)/PE (Pulmonary Embolism)/VTE (Venous Thromboembolism); Malignancy – type and grade.

Primary outcomes:

- Clinical response rate (decrease in the partial Mayo score by 2 or partial Mayo score <2) at end of induction (week 8-12) and week 16.

Secondary endpoints:

- Remission rate (decrease in the partial Mayo score to <2 with no individual sub score greater than 1) at end of induction (week 8-12) and week 16.
- Proportion of patients initiated on tofacitinib completing induction therapy (8 or 16 weeks).
- Persistence of response up to week 52 – This will be analysed using a time dependent Kaplan-Meier survival curves.
- Resolution of rectal bleeding at end of induction (Mayo rectal bleeding score = 0).
- Endoscopic healing in those who had endoscopy (Mayo endoscopic score 0 or 1).
- Cessation of steroids in those on steroids at commencement of tofacitinib (proportion of patients who cease steroid who were on a dose equivalent of >10 mg prednisone at the time of initiation of tofacitinib).
- Steroid free clinical remission at end of induction and at week 48 (decrease in the partial Mayo score to <2 with no individual sub score greater than 1).

- Change in CRP (C-reactive protein) and calprotectin (per patient delta) for patients with baseline and follow-up results.
- Change in cholesterol, LDL (Low Density Lipoprotein) and HDL (High Density Lipoprotein) when measured (per patient delta).
- Colectomy rate.

9. RESEARCH METHODS

9.1. Study Design

This is a longitudinal, retrospective, non-interventional. multi-center observational study. It will involve secondary data collection (of unstructured data) from patient charts. Data will be collected from multiple centres which were using tofacitinib for ulcerative colitis in their routine clinical practice. The patients who required drug as deemed by their treating physicians were given access to on-label tofacitinib by Pfizer before PBS approval and will be part of this study. Patients with atleast 16 weeks of follow-up will be included in the analysis. The de-identified data will be extracted from the start of early access of tofacitinib to Australian UC patients (Feb 2019) to end of data collection (July 2022) which will be the sample window.

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

9.2. Setting

The deidentified data will be extracted from the individual patient chart review by centres/hospitals using early access tofacitinib for ulcerative colitis and agreeing to participate in this observational study. Mater research will be the lead site co-ordinating with these individual sites. The prospective HREC (Human Research Ethics Committee) approval will be required and will be managed by Mater research. After all required approvals the data collection will start. The sample window will be from the start of early access of on-label tofacitinib to Australian UC patients (Feb 2019) to end of data collection (July 2022). Patients across Australian centres who were granted access to tofacitinib since TGA listing in February 2019; patients with an established diagnosis of Ulcerative Colitis; ≥18 years of age; with a minimum of 16 weeks of follow-up data and up to 52 weeks and meeting inclusion/exclusion criteria will be included in this study. The end of follow up will be data upto 52 weeks or upto tofacitinib discontinuation for any reason.

The CRFs (case report forms) will be shared by Mater research to the individual sites and collected again by Mater. This will be a one time activity. The data will be deidentified and patient names will be replaced by a single, specific, numerical code, based on a numbering system.

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9.2.1. Inclusion Criteria

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

- Patients who were granted access to tofacitinib since TGA listing in February 2019;
- Patients with an established diagnosis of Ulcerative Colitis;
- ≥18 years of age;
- At least 16 weeks of patient safety follow-up, and up to 52 weeks;
- Used tofacitinib as per the Xeljanz Australian PI (Package Insert)/label and met Pfizer inclusion criteria for grant of early access to tofacitinib before PBS listing; ie,
    - UC patients who were in-adequate responders or intolerant to conventional or biologic therapies.

or

- Patients who are meeting one of the scenarios below
    - Facing an imminent colectomy;
    - Intolerant or did not respond to 1 biologic, with severe disease and facing colectomy (considering no other available PBS listed drug is an option);
    - Intolerant or did not respond to 2 approved biologics of different mode of actions;
    - Or if patients had previous toxicity reportings to biologics (anti-TNFs, anti-intergins, or anti-interleukins) and cannot use them.

9.2.2. Exclusion Criteria

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

1. Patients not eligible to receive on-label tofacitinib for UC treatment after internal medical analysis, before reimbursement in Australia.

9.3. Variables

Data collection will encompass demographics (age, gender, ethnicity), Montreal classification (disease extent and worst ever severity), disease duration, disease activity at time of tofacitinib commencement, partial Mayo Score, previous therapies (5-ASA or 5- Aminosalicylic Acid, thiopurine, anti-TNF, anti-integrin or anti-interleukins, recent endoscopic severity, current steroid use (dose), inflammatory markers where available (CRP, calpro, ESR or Erythrocyte Sedimentation Rate), lipids (if measured), tofacitinib dosing regimen, SAE/AEs during treatment (hospitalisation, infectious complications, incidence of Zoster an extent (one dermatome, multiple dermatomes, ocular, systemic disease), MACE, DVT /PE, NMSC (Non-Melanoma Skin Cancer), malignancies.

9.3.1. Baseline

- Demographics (age, gender, ethnicity).
- Physical examination (height, weight, calculated body mass index, waist circumference, smoking status [current/quit <1yr/former/never/unknown]).
- Montreal classification (disease extent and worst ever severity).
- Disease duration.
- Disease activity at time of tofacitinib commencement (Partial Mayo Score).
- Concomitant ulcerative colitis therapies.
- Current steroid use (dose).
- Previous therapies (5-ASA, thiopurine, anti-TNF, anti-integrin or anti-interleukins). Number, sequence and duration of previous therapies (if available).
- Most recent endoscopic severity (MES).
- Inflammatory markers where available (CRP, calprotectin).
- Lipids if measured at baseline.
- Other relevant medical history and co-morbidities (specify, date of diagnosis, end date [if applicable]), including:
    - History of venous thromboembolism (VTE) (date of event, type of event [deep venous thrombosis, pulmonary embolism]);
    - Myocardial infarction within previous 3 months (date of event, type of event [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), unknown]);
    - Diagnosis of heart failure (date of diagnosis);
    - Diabetes (date of diagnosis, specify [type 2/type 1]);
    - Hypertension (date of diagnosis, treated [Yes/No/unknown], treatment resistant [Yes/No/unknown]);
    - Inherited coagulation disorder (date of diagnosis, specify);

- Malignancy (date of diagnosis, specify);
- Use of combined hormonal contraceptives or hormone replacement therapy (generic name, start/end date, reason for discontinuation [if applicable]);
- Any other relevant medical history.

9.3.2. Week 8/12, 16, 24 and 52

- Tofacitinib dosing (dosage, start/stop dates, reason for discontinuation [if applicable]).
- Concomitant UC treatment (generic name, dose, start/stop dates, reason for discontinuation [if applicable]).
- Relevant co-morbidities (specify, date of diagnosis, end date [if applicable]).
- Physical examination (weight, calculated body mass index, waist circumference, smoking status [current/quit <1yr/former/never/unknown]).
- Inflammatory markers where available (CRP, calprotectin).
- Montreal classification (disease extent and worst ever severity).
- Disease activity at time (Partial Mayo Score).
- Lipid levels if available.
- SAE/AE's during treatment – including AE's of special interest:
  - Hospitalisation;
  - Infectious complications/Serious infections, Opportunistic Infections;
  - Incidence of Herpes Zoster and extent (one or multiple dermatomes, ocular, systemic disease);
  - MACE;
  - DVT/PE/VTE;
  - Malignancy – type and grade.

Table 2. Baseline and Outcome Variables

Variable	Role	Data source(s)	Operational definition
Patient characteristics	Baseline characteristic	Patient charts	Age, gender, ethnicity and presence of comorbidities, physical examination
Clinical characteristics	Baseline characteristic	Patient charts	Disease duration, disease severity, disease activity (Montreal classification, partial mayo score, MES, CRP, calprotectin), safety events (AEs, SAEs, infections, relevant labs, CV events, malignancy)
Treatment history	Baseline characteristic, potential confounder	Patient charts	Number, sequence and duration of previous therapies (if available)
Concomitant therapy	Baseline characteristic, potential confounder	Patient charts	Type and dose of concomitant therapies
Treatment duration	Outcome	Patient charts	Duration of treatment of the index therapy (Tofacitinib)
Clinical characteristics	Outcome	Patient charts	Disease activity (Montreal classification, partial mayo score, MES, CRP, calprotectin), safety events (AEs, SAEs, infections, relevant labs, CV (cardiovascular) events, malignancy)

9.4. Data Sources

All data for this study will be obtained from individual patient charts from routine clinical practice. Data will be collected using case report forms. The deidentified data will be collected from each site/investigator and will be processed for further analysis.

9.4.1. Physical Assessments

Partial mayo score*

Stool frequency†:

0 = Normal number of bowel movements for this patient.

1 = 1 to 2 bowel movements more than normal.

2 = 3 to 4 bowel movements more than normal.

3 = 5 or more bowel movements more than normal.

Subscore, 0 to 3.

Rectal bleeding‡:

0 = No blood seen.

1 = Streaks of blood with stool less than half the time.

2 = Obvious blood with stool most of the time.

3 = Blood alone passes.

Subscore, 0 to 3.

Physician's global assessment§:

0 = Normal.

1 = Mild disease.

2 = Moderate disease.

3 = Severe disease.

Subscore, 0 to 3.

* The partial Mayo score ranges from 0 to 9, with higher scores indicating more severe disease.[10]

† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

‡ The daily bleeding score represents the most severe bleeding of the day.

§ The physician's global assessment acknowledges the three other criteria, the patient's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

Remission = 0-1 Mild Disease = 2-4 Moderate Disease = 5-6 Severe Disease =7-9, response - clinical response was a decrease from baseline in the partial Mayo Score ≥2 points.[11]

9.5. Study Size

The expected sample size is 250 patients.

Power calculation – assuming $\alpha = 0.01$ and 90% power, 160 participants would be required to observe a minimum clinical difference between the published response rates for clinical response between placebo and tofacitinib. Fewer patients would also be adequate for analysis involving 80% power.

9.6. Data Management

9.6.1. Case Report Forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF 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.

A CRF is required and should be completed for each included patient. The completed original CRFs 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 are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

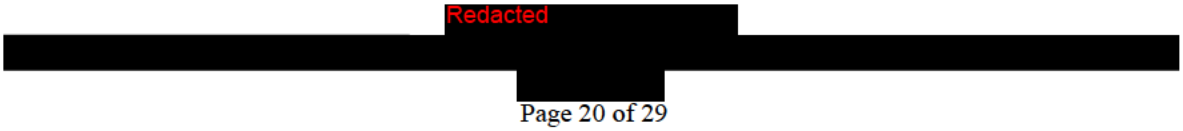
The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely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

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.



Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, or as required by applicable local regulations.

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

9.7. Data Analysis

Baseline has been defined in Section 9.2.

Descriptive summary statistics for continuous variables will be used to describe the study population including number of participants, mean, standard deviation, median and range. Categorical variables will be described with frequency counts and percentages. Pre-specified groups for statistical analysis include remitters, responders, and non-responders at the specified time points. P values will be calculated from chi-square for categorical variables and t-tests for continuous variables with normal distribution and non-parametric testing for non-normally distributed data. Kaplan-Meier survival analyses will be used to analyse individual predictors and display survival curves. Cox proportional hazards regression will be used to analyse multivariable survival data. Purposeful selection will be used to create a multivariable model by including variables from the univariate analysis with a p-value <0.10. Variables will then be excluded from this model that do not reach significance ($p<0.05$). Excluded variables will be added back to the model one at a time to check for confounding. Hazard ratios and 95% confidence intervals will be reported. Logistic regression, adjusting for relevant covariates will be used to define odds ratio's (95% confidence intervals (CI)) to assess risk of disease flare during the period of the study and while participants are on tofacitinib treatment.

Imputation: Patients withdrawing from study due to inefficacy/non-response and AEs will be considered as non-responders. Patients who had intermediate missing values, linear extrapolation will be used to replace such values. Patients not discontinuing but with missing last evaluation at year 1, both LOCF (Last Observation Carried Forward) and NRI (Non Responder Imputation) will be used and compared.

9.7.1. Patient Demographics

Patient demographics will be summarised descriptively.

9.7.2. Treatment Patterns

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

9.7.3. Clinical Effectiveness

Measures to be made according to data collected from CRFs.

9.7.4. Safety

Descriptive analysis of the most common/frequent adverse events will be performed.

9.8. Quality Control

Data quality will be assessed by the lead institute to ensure completeness, and verified with the contributing sites where required. In addition, the lead site research governance office will perform monitoring activities as required.

9.9. Limitations of the Research Methods

This is a retrospective study based on data collected from individual doctors. The analyses are therefore limited by the availability of data. The analysis is limited by low sample size.

The safety information is based on the voluntary reporting.

The source data will be subject to logic checks 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

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.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site 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, the study site 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, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will

maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

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

10.3. Institutional Review Board (IRB)/Independent ethics committee (IEC)/Human Research Ethics Committee

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant HREC/IRBs/IECs. All correspondence with the HREC/IRB/IEC must be retained. Copies of HREC/IRB/IEC approvals must be forwarded to Pfizer.

This study is low risk research as determined by the local guidelines (National Health and Medical Research Council, NHMRC guidelines.). It will require review by human research advisory panel and also require research governance. The copies of review will be shared with Pfizer.

10.4. Ethical Conduct of the Study

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 (AEs) 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 data collection tool (eg, chart abstraction 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 AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must 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 trainings 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.

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 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

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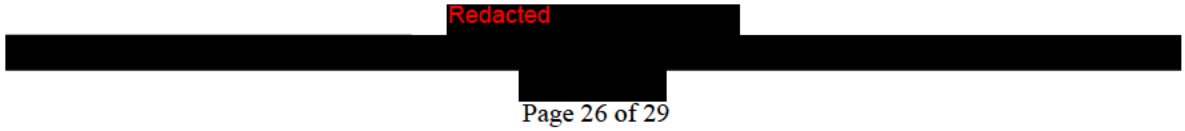

14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	23 September 2021	***Early access tofacitinib use in Australia: an observational study***

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

List of proposed sites.

(#)	Institute	State	Private/Public
1	St Vincent's Hospital	VIC	Private
2	Austin Health	VIC	Public
3	St John of God	WA	Private
4	Mater Hospital	QLD	Private
5	St Vincent's Hospital	NSW	Private
6	Concord Hospital	NSW	Public
7	Eastern Health	VIC	Public
8	Gold Coast Health	QLD	Public
9	Royal Melbourne Hospital	VIC	Public
10	Monash Health	VIC	Public
11	Flinders Medical Centre	SA	Public
12	Alfred health	VIC	Public
13	Sunshine Coast University Hospital	QLD	Public
14	Fiona Stanley Hospital	WA	Public
15	Port Macquarie Gastroenterology & Endoscopy	NSW	Private
16	Liverpool Hospital	NSW	Public
17	St Vincent's Hospital	NSW	Public
18	Wollongong Public Hospital	NSW	Public
19	Kanwal Medical Centre	NSW	Private
20	Lyell McEwin Hospital	SA	Public
21	St John of God, Bendigo	VIC	Private
22	St Vincent's Hospital	VIC	Public
23	U75 Wexford Medical Centre	WA	Public
24	Cabrini Hospital	VIC	Private
25	Macquarie University Hospital	NSW	Private
26	Mater Hill Gastroenterology	QLD	Private
27	Nepean Public Hospital	NSW	Public
28	Northern Hospital	VIC	Public
29	QE2 Hospital	QLD	Public
30	Royal Brisbane and Women's Hospital	QLD	Public
31	Blacktown Hospital	NSW	Public
32	Royal Darwin Hospital	NT	Public
33	Calvary Hospital	TAS	Private
34	Brindabella Specialist Centre	ACT	Public
35	The Calvary Clinic	ACT	Private

Redacted

(#)	Institute	State	Private/Public
36	Glen Iris Private	VIC	Private
37	Nepean Private Specialist Centre	NSW	Private
38	Royal Adelaide Hospital	SA	Public
39	RPA Hospital, Sydney	NSW	Public
40	Werribee Mercy Health	VIC	Public
41	GS Tasmania	TAS	Private

Redacted

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