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

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
Version identifier of the study report	1.0
Date	29 September 2025
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.
Country(-ies) of study	Australia
Author	Dr/Prof Jakob Begun, MD PhD IBD Group Leader, Mater Research Ltd, Director of Gastroenterology at Mater Hospital Department of Gastroenterology, Salmon Building, Level 4, Raymond Terrace, South Brisbane, Qld 4101 Dr Amit V. Thorat, MBBS MHA MPharmMed Inflammation & Immunology Medical Affairs, Pfizer Australia Mezzanine Level 1, 525 Collins Street, Melbourne, VIC, 3000 Australia

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Appendix 2.1 PROTOCOL

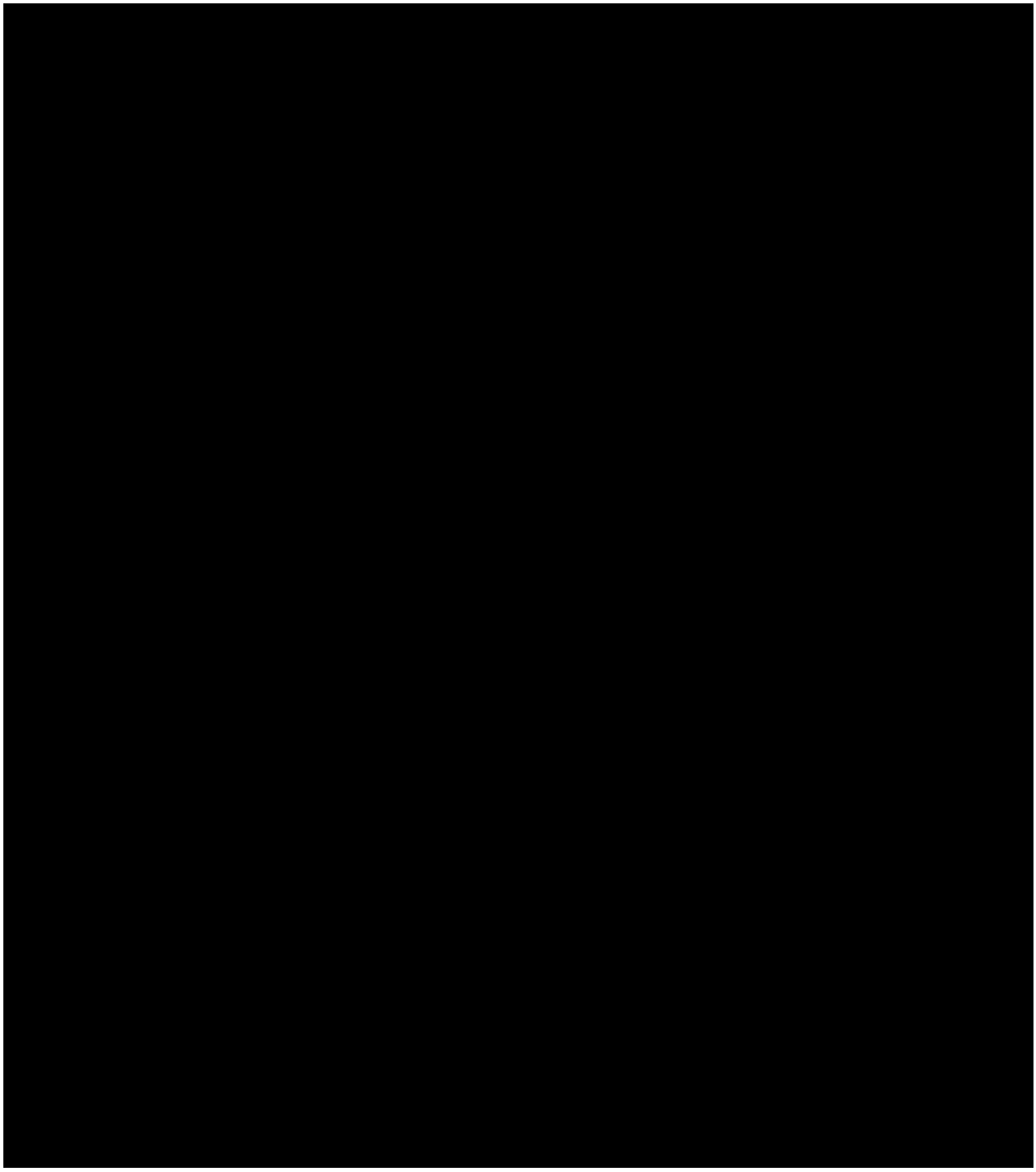
Document Name	Version	Date
A3921405_Non-Interventional Study Protocol_V3.0_15AUG2024	3.0	15 August 2024
A3921405 Protocol V2.0 23rd September 2021 (Clean)	2.0	23 September 2021

Appendix 2.2 Protocol administrative change letter (PACL)

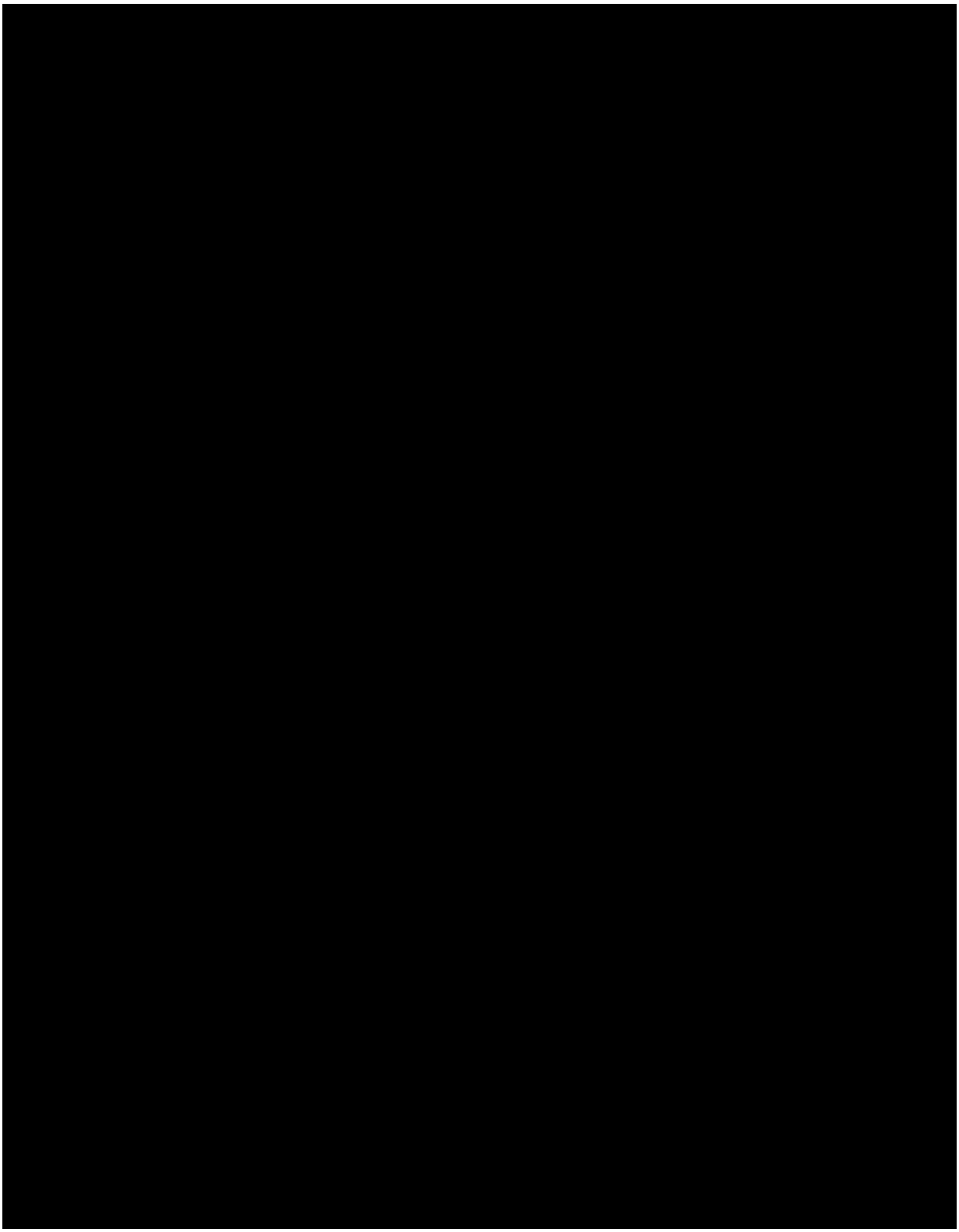
Not applicable

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

Appendix 3.1. List of Investigators by Country



Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates



Appendix 4. STATISTICAL ANALYSIS PLAN

Document Name	Version	Date
A3921405_Statistical Analysis Plan (SAP)_V1.0_15AUG2024_Final	1.0	15-AUG-2024

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT)

Document Name	Version	Date
Tofa UC Data Collection – Mater	-	-

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable.

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Appendix 7.1 Withdrawn Subjects

Not applicable.

Appendix 7.2 Protocol Deviations

None.

Appendix 7.3 Subjects Excluded from the Analysis

Not applicable.

Appendix 7.4 Demographic Data

Table 1. Baseline patient demographics

Demographics, n (%)	Overall Cohort (n=124)	Standard Induction (n=50)	Extended Induction (n=74)	p-value
Female	51 (41)	25 (50)	26 (36)	0.07
Median age at time of induction, years (IQR)	41 (25- 53)	46 (27-57)	35 (23 -50)	0.09
Disease duration, years (IQR)	9 (3-11)	10 (3-12)	9 (4-11)	0.25
Montreal classification – disease extent				0.89
E1 – proctitis	12 (10)	4 (8)	8 (11)	
E2 – left-sided UC	53 (43)	21 (43)	32 (43)	
E3 – extensive UC	59 (47)	24 (49)	35 (47)	
Montreal classification – endoscopic disease severity				0.04
S1 – mild	25 (20)	13 (27)	12 (18)	
S2 – moderate	50 (40)	16 (32)	33 (45)	
S3 – severe	49 (40)	21 (42)	29 (39)	
Current smoker	8 (6)	5 (10)	3 (4)	0.08

Number of prior Advanced Drug Therapies				0.34
0	10 (8)	2 (4)	8 (10)	
1	44 (36)	18 (36)	26 (35)	
2	57 (46)	25 (50)	32 (42)	
≥ 3	13 (10)	6 (11)	7 (10)	
Prior Advanced Drug Therapy				
Anti-TNF	104 (84)	44 (89)	60 (80)	0.14
Anti-Integrin	76 (61)	32 (65)	44 (59)	0.42
Il-12/23	22 (17)	9 (18)	13 (17)	0.85
Baseline concomitant medications				
Oral corticosteroid	35 (28)	14 (28)	21 (28)	0.92
Oral 5-ASA	79 (63)	33 (67)	46 (62)	0.61
Median Baseline CRP (IQR)	7 (2-17)	6 (2-15)	7 (2-14)	0.93
Median Baseline FCP (IQR)	645 (175-1219)	651 (145 – 1142)	632 (193-1371)	0.87
Median Baseline Mayo endoscopic subscore (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	0.95

Appendix 7.5 Medication/Treatment Data

Refer to Appendix 7.4 Demographic Data.

Appendix 7.6 Endpoint Data

Table 2. Primary and Secondary Outcomes

Overall Primary and Secondary Outcomes, n/N (%)	Baseline	Week 8	Week 16	Week 52
Clinical Response	-	78/112 (70)	67/112 (60)	62/91 (68)
Clinical Remission	12/124 (9)	68/124 (55)	64/124 (52)	56/91 (62)
Corticosteroid-free Clinical Remission	-	16/35 (46)	14/35 (40)	13/20 (65)
Resolution of Rectal Bleeding	-	46/91 (50)	37/91 (41)	29/62 (47)
Resolution of Stool Frequency	-	22/109 (21)	28/109 (26)	19/72 (26)
Biochemical Remission	41/117 (33)	44/76 (58)	46/76 (61)	28/54 (52)
Endoscopic Healing	-	19/35 (54)	37/59 (63)	36/76 (47)
Colectomy rate	-	1/124 (1)	2/124 (2)	2/91 (3)

Appendix 7.7 Adverse Events

Table 3. Adverse Events

Adverse Event, n patients (%)	Overall Cohort (n=124)	Standard Induction (n=50)	Extended Induction (n=74)
Total Adverse Events	21 (17)	8 (16)	13 (18)
Acne	6 (5)	4 (8)	2 (3)
Herpes Zoster infection	6 (5)	3 (6)	3 (6)
Headache	4 (3)	2 (4)	2 (3)
Nasopharyngitis	4 (3)	2 (4)	2 (3)
Serious Adverse Events	9 (7)	4 (8)	5 (7)
Severe infection	1 (0)	0 (0)	1 (2)
Colectomy	2 (2)	1 (2)	1 (2)
Patients with multiple Adverse events	5 (4)	2 (2)	3 (3)
MACE	0 (0)	0 (0)	0 (0)
Malignancy	1 (1)	1 (2)	0 (0)
VTE	0 (0)	0 (0)	0 (0)

Appendix 7.8 Laboratory listings

Not applicable.

Appendix 8. ADDITIONAL DOCUMENTS

Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

Document Name	Version	Date
A3921405_Study Report Abstract_V1.0_29Sep2025	1.0	29 September 2025

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ADT	Advance Drug Treatment
ASUC	Acute Severe Ulcerative Colitis
5-ASA	5- Amino salicylic Acid
CFCR	Corticosteroid Free Clinical Remission
CI	Confidence Interval
CRF	Case Report Form
CRP	C-reactive protein
CV	Cardiovascular
DCT	Data Collection Tool
DVT	Deep Vein Thrombosis
ESR	Erythrocyte Sedimentation Rate
FCP	Fecal Calprotectin
GPP	Guidelines For Good Pharmacoepidemiology Practices
HDL	High Density Lipoprotein
HZ	Herpes Zoster
PACL	Protocol administrative change letter

HREC	Human Research Ethics Committee
IBD	Inflammatory Bowel Disease
ICD	Informed consent document
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society For Pharmacoepidemiology
IQR	Interquartile Range
LDL	Low Density Lipoprotein
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
PASS	Post-Authorization Safety Study
PBS	Pharmaceutical Benefit Scheme
PE	Pulmonary Embolism
PI	Package Insert
RGO	Research Governance Office
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TGA	Therapeutic Goods Administration
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
UK	United Kingdom

USA	United States of America
VTE	Venous thromboembolism

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

3.1. Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Dr/Prof Jakob Begun, MD PhD	IBD Group Leader, Mater Research Ltd, Director of Gastroenterology at Mater Hospital	Mater Research and Hospital
Dr Yoon-Kyo An, BMedSc MBBS FRACP	Clinical Lead in IBD Clinical Trials unit at Mater Research, Head of Inflammatory Bowel Disease at Mater Hospital	Mater Research and Hospital
Dr Amit Thorat, MBBS MHA MPharmMed	NI Study Lead	Medical Affairs, Pfizer Australia
Candida Da Fonseca Pereira, PhD	NI Study co-lead	Medical Affairs, Pfizer Australia

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Dr/Prof Jakob Begun, MD PhD	IBD Group Leader, Mater Research Ltd, Director of Gastroenterology at Mater Hospital	Mater Research and Hospital
Dr Amit Thorat, MBBS MHA MPharmMed	NI Study Lead	Medical Affairs, Pfizer Australia

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual Date
Start of data collection	22 October 2021	11 March 2022
End of data collection	08 July 2022	27 February 2024
Registration in the HMA-EMA Catalogues of RWD Studies	30 September 2021	30 September 2021
Final report of study results	19 August 2022	30 September 2024

6. 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 benefit 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 (NIS) will address this data gap as well as add to the real-world evidence already published.

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

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

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Research Question:

Examine the disease characteristics and outcomes in UC 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.

7.2. 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 (HZ) 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 endpoint:

- 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 analyzed 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.

8. AMENDMENTS AND UPDATES

Table 4. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
2	23 September 2021	Administrative	Title Page and Section 3 Responsible Parties	Title of Dr/Prof Jakob Begun, MD PhD changed from IBD Group Leader, Mater Research Ltd, Clinical lead in IBD (Inflammatory Bowel Disease) at Mater Hospital to IBD Group Leader, Mater Research Ltd, Director of Gastroenterology at Mater Hospital.	Administrative
		Administrative	Section 3 Responsible Parties	Title of Dr Yoon-Kyo An, BMedSc MBBS FRACP changed from Clinical Lead in IBD Clinical Trials unit at Mater Research, Gastroenterologist at Mater Hospital to Clinical Lead in IBD Clinical Trials unit at Mater Research, Head of Inflammatory	Administrative

				Bowel Disease	

				at Mater Hospital.	
		Administrative	Section 3 Responsible Parties	Address of Dr Amit Thorat, MBBS MHA MPharmMed changed from 3rd Floor, 500 Collins Street, Melbourne, VIC, 3000 Australia to Mezzanine Level 1, 525 Collins Street, Melbourne, VIC, 3000 Australia.	Administrative
		Administrative	Annex 1. Stand Alone Documents	Change in Annex 1 (abstract) version date.	Administrative
		Administrative	Annex 3. Additional Information	List of proposed sites added in Annex	Administrative
3	15 August 2024	Administrative	Title page	NI Study Lead role changed from Dr. Mauricio Andrade to Dr. Amit Thorat.	Administrative
3	15 August 2024	Administrative	Section 6	Milestones updated	Administrative
3	15 August 2024	Administrative	Section 8.2	Primary outcome renamed as Primary endpoint	Administrative
3	15 August 2024	Substantial	Section 9.5	Sample size updated and rationale for update added	Administrative
3	15 August 2024	Administrative	Section 9.5	Statistical rationale for sample size removed	Administrative
3	15 August 2024	Administrative	Section 9.6.2	Record retention timelines updated as per new guidelines	Administrative

3	15 August 2024	Administrative	Section 9.7	Modified to reflect addition of separate SAP	Administrative
3	15 August 2024	Administrative	Section 9.7	Modified to reflect changes in data analysis considering changes to recruitment size.	Administrative
3	15 August 2024	Administrative	Section 11	Section modified to reflect the latest standard safety language for the study	Administrative
3	15 August 2024	Administrative	Annexure 3	Study sites updated	Administrative
3	15 August 2024	Administrative	Section 3 Responsible Parties	Added Candida Da Fonseca Pereira as study co-lead	Administrative

9. RESEARCH METHODS

9.1. Study design

This is a longitudinal, retrospective, non-interventional. multi-centre observational study. It involves secondary data collection (of unstructured data) from patient charts. Data was 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 are part of this study. Patients with at least 16 weeks of follow-up are included in the analysis. The de-identified data was extracted from inflammatory bowel disease centres who commenced tofacitinib for UC between February 2019 and July 2022 via the patient familiarisation program (PFP).

9.2. Setting

The deidentified data was 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 is the lead site co-ordinating with these individual sites. The prospective HREC (Human Research Ethics Committee) approval is required and managed by Mater research. After all required approvals the data collection started. The sample window was from the start of early access of on-label tofacitinib to Australian UC patients (February 2019) to end patient familiarization program(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 are included in this study. The end of follow up are data up to 52 weeks or up to tofacitinib discontinuation for any reason.

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

9.3. Subjects

9.3.1. 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 UC;
- ⩾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 reporting to biologics (anti-TNFs, anti-integrins, or anti-interleukins) and cannot use them.

9.3.2. 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.

9.4. Variables

Data collection encompassed 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, FCP, ESR or Erythrocyte Sedimentation Rate), lipids (if measured), tofacitinib dosing regimen, SAE/AEs during treatment (hospitalization, infectious complications, incidence of Zoster an extent (one dermatome, multiple dermatomes, ocular, systemic disease), MACE, DVT /PE, NMSC (Non-Melanoma Skin Cancer), malignancies.

9.5. Data sources and measurement

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

Demographic and clinical data were collected by retrospective chart review. The following demographic data was collected: age at induction, sex, smoking history, age at diagnosis, disease duration, extent of disease, prior endoscopic severity, surgical history, presence of extra-intestinal manifestations, prior and current medications including prior ADT (Advance Drug Treatment) exposure (defined as loss of response as per treating clinician with biologic or small molecule therapies). All prior IBD medications were documented, with current usage defined as any use within 8 weeks prior to tofacitinib induction. Concurrent medications, including corticosteroids and their cumulative doses, were documented throughout the follow-up period.

Clinical, biochemical, and endoscopic data were collected at set time points: baseline (prior to commencement of tofacitinib), week 8 (+/- 14 days), week 16 (+/- 14 days) and week 52 (+/- 28 days) post commencement of tofacitinib therapy. All endoscopic assessments throughout the 52-week follow-up were collected, including both Mayo endoscopic subscore and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scores.

9.6. Bias

This study has limitations inherent to its retrospective design, including the potential for recall bias which, although mitigated by the inclusion of all consecutively treated patients, is an unavoidable risk.

9.7. Study Size

Sample size calculations are not applicable as it is a descriptive study, and no prior hypothesis are specified. The number of patients eligible for this study were 124.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 4).

9.9. Statistical methods

As cited in the SAP section 4.8 in Appendix 4.

9.9.1. Main summary measures

Continuous variables were summarized with medians with interquartile ranges (IQRs). Comparison between groups of continuous parametric variables were conducted using the Student's t-test, while the Wilcoxon rank-sum test was applied for nonparametric variables. Categoric variables were presented as counts and percentage, with group comparisons performed using the chi-squared test.

9.9.2. Main statistical methods

Effectiveness: Categorical endpoints are described by frequency distribution while continuous endpoints expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate. In general, all data are listed, sorted by site, treatment and subject.

Summary statistics (N, n, %, 95% CI) by visit and treatment for binary endpoints i.e Clinical response rate (decrease in the partial Mayo score by 2 or partial Mayo score <2) & remission rate (decrease in the partial Mayo score to <2 with no individual sub score greater than 1), proportion of patients completing induction therapy, resolution of rectal bleeding (Mayo rectal bleeding score = 0), Endoscopic healing (Mayo endoscopic score 0 or 1), cessation of steroids in those on steroids at commencement of tofacitinib and steroid free clinical remission, colectomy rate at weeks 8, 12, 16, 24, 52.

Descriptive statistics (n, mean, standard deviation, standard error, minimum, 1st quartile, median, 3rd quartile, maximum, 95% confidence interval for mean) by visit and treatment for continuous endpoints like partial Mayo score, CRP, Faecal calprotectin change from baseline, proportion of patients on treatment.

Kaplan-Meier survival analyses are used to display survival curves.

All summary tables are structured with a column for 'tofacitinib group'. The mean, standard deviation, and any other statistics other than quantiles, are reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum use the same number of decimal places as the original data.

All analyses are descriptive and there are no comparative analyses being undertaken, therefore, no adjustments for multiple data cuts and multiple endpoints are required. All variables listed in Section 4 are summarized for the overall population, Index date and follow-up.

There is an analysis of covariates that differ between remitters and non-remitters, as well as responders and non-responders, noting that these analyses are explorative and descriptive

in nature and conclusion cannot be drawn considering small sample size. These analyses only explain the trends with quoting limitations of sample size.

Safety: Descriptive analysis of the most common/frequent adverse events are performed. The AEs are expressed as % (number of subjects with events/number of subjects exposed)

Imputation: Since the analysis is descriptive, imputation of data will not be done. Summary statistics are used on completed cases. No adjustment of confounders to be done.

9.9.3. Missing values

None.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

Data quality is 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.

9.11. Protection of human subjects

Subject information and consent

Not Applicable.

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

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.

Ethical conduct of the study

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

10. RESULTS

10.1. Participants

Table 5.. Number of participants

	Potentially eligible	Confirmed eligible
Number of Participants	126	124

Eligible participants were adults (≥18 years) with a confirmed diagnosis of UC for at least 3 months. Patients must have completed at least 16 weeks of tofacitinib therapy for moderate to severe UC or had discontinued treatment within the 16 week induction period due to lack of response, adverse events, or other reasons. Available data up to 52 weeks after commencement of tofacitinib was collected. Patients with indeterminate colitis, Crohn's disease, prior colectomy including pouchitis, pregnancy, breastfeeding, recent venous thromboembolism ormalignancy within 5 years were excluded.

10.2. Descriptive data

A total of 124 patients met inclusion criteria and were included in the analysis. The clinical and demographic characteristics of the cohort are summarized in Table 1. The median age was 41 years (IQR 29-49), 41% were female, with a median disease duration of 9 years (IQR 5-14), with 6% actively smoking. Disease extent included isolated proctitis (E1) in 10% (n=12), left-sided colitis (E2) in 43% (n=53), and extensive colitis (E3) in 47% (n=59). The median baseline partial Mayo score was 5 (IQR 3-6).

Tofacitinib was used as a first-line advanced drug therapy in 8% (n=10) of patients, leaving 92% (n=112) of patients exposed to at least 1 prior ADT. Of these 36% (n=44) had prior exposure to one ADT, 46% (n=57) to two ADTs, and 10% (n=13) to three or more ADTs. Drug specific ADT exposure included anti-TNF therapy in 84% (n=104), vedolizumab in 61% (n=76) and ustekinumab in 18% (n=22).

During induction, tofacitinib was given concomitantly with oral corticosteroids in 28% of patients, with oral aminosalicylates in 63%, and 21% received both corticosteroids and aminosalicylates. All patients received tofacitinib induction therapy of 10mg twice daily for a minimum of 8 weeks. Following this initial induction period, 60% (74 of 124) continued with extended induction of 10mg twice daily for an additional 8 weeks at the discretion of the treating clinician, while the remaining patients reduced to 5mg twice daily (summarized in Table 1). While most patients transitioned to a maintenance dose of 5mg twice daily for the remainder of the study, 5 patients who continued an escalated dose of 10mg twice daily were excluded from the analysis.

10.3. Outcome data

Biochemical Outcomes

Complete biochemical data at baseline and within the first 16 weeks of follow up were available for 117 patients (Table 2). The median CRP level decreased from 7 mg/L (IQR 2-17) at baseline to 4 mg/L (IQR 1-8) at week 8, and further to 2 mg/L (IQR 1-7) at week 16. The median FCP level also decreased from 645 µg/g (IQR 175-1440) at baseline to 171 µg/g (IQR 17-495) at week 8, and further to 143 µg/g (IQR 24-346) at week 16. At baseline, 35% (41 of 117) met criteria for biochemical remission. Of those with significantly elevated FCP or CRP at baseline (defined by levels of either >50 ug/g or >6.0 mg/L respectively), 58% (44 of 76) achieved biochemical remission at week at 8, 61% (46 of 76) by week 16
and 54% (26 of 48) by week 52.

In the standard induction cohort, 63% (20 of 32) achieved biochemical remission at week 8, 56% (18 of 32) at week 16, and 55% (12 of 22) at week 52. In the extended induction cohort, 56% (25 of 44) achieved biochemical remission at week 8, 68% (30 of 44) at week 16, and 54% (14 of 26) at week 52. There was no significant difference in rate of biochemical remission at any timepoint between the cohorts (week 8 p=0.34, week 16 p=0.15, week 52 p=0.43)

Endoscopic Outcomes

Among the 93 patients who underwent baseline endoscopy within 1 month of tofacitinib induction, 59 had a repeat endoscopy at week 16 and 76 at week 52. The baseline median Mayo endoscopic subscore was 2 (IQR 2-3), which reduced to 1 (IQR 0-1) at week 16 and 1 (IQR 0-2) at week 52. Endoscopic remission (MES of 0-1) observed in 63% (37 of 59) of patients at week 16 and 47% (36 of 76) at week 52.

In the standard induction cohort, 54% (15 of 28) achieved endoscopic remission at week 16, and 41% (14 of 34) at week 52. In the extended induction cohort, 68% (21 of 31) achieved endoscopic remission at week 16, and 50% (21 of 42) at week 52. There was no significant difference in rate of biochemical remission at any timepoint between the cohorts (week 16 p=0.09, week 52 p=0.21)

10.4. Main results

Overall Clinical Effectiveness

Complete clinical data at both weeks 8 and 16 were available for all 124 patients and included during analysis of standard and extended induction sub-group clinical response. Patients who met criteria for moderate to severe disease at baseline (112 of 124) were only included for analysis of clinical response in overall population. The 12 excluded patients had mild to moderate disease but switched to tofacitinib therapy due to prior medication intolerance or patient and physician preference.

The primary endpoint of clinical response was achieved by 70% (78 of 112) of patients at

week 8, and 60% (67 of 112) at week 16 following tofacitinib initiation in patients with moderate to severe colitis activity at baseline (Figure 1). Clinical remission was observed in 55% (68 of 124) of patients at week 8 and 52% (64 of 124) at week 16.

At week 52, clinical data were available for 91 patients (73% of the cohort), with the remaining patients either lost to (8%) or yet to complete 1 year of follow-up (19%) at time of data collection. The 21 patients who discontinued tofacitinib during follow-up as treatment failures were included using non-response imputation. Clinical response rate was 68% (62 of 91) and remission rate was 62% (56 of 91) (Table 2).

In the subset of 91 patients presenting with rectal bleeding at baseline, 50% (46 of 91) achieved complete resolution by week 8, 41% (37 of 91) by week 16, and 75% (47 of 63) by week 52. Of the 109 patients with increased stool frequency at baseline, 21% (23 of 109) had complete resolution by week 8, 26% (28 of 109) by week 16, and 59% (37 of 63) by week 52.

There were 35 patients receiving concomitant corticosteroid during induction. Among these, CFCR was achieved in 46% (16 of 35) at week 8 and 40% (14 of 35) patients at week 16. By week 52 no patients remained on corticosteroid, with an improvement in CFCR to 65% (13 of 20).

12 patients with ulcerative proctitis were treated with tofacitinib, with 83% (10 of 12) achieving clinical response by week 8 and 92% (11 of 12) by week 16. Clinical remission rates were also high in this cohort at 58% at week 8 (7 of 12) and 83% (10 of 12) by week 16. Clinical response (73%) and remission rates (73%) remained high throughout 52 weeks of follow- up.

Standard vs Extended Induction

Among the 50 patients who received standard induction, 70% (35 of 50) achieved clinical response and 58% (29 of 50) achieved clinical remission at week 8. By week 16 (after 8 weeks of dose reduction to 5mg twice daily), only 46% (23 of 50) met criteria for clinical response and 44% (22 of 50) for clinical remission. By week 52, data was available for 35 of those 50 patients, 54% (19 of 35) met criteria for clinical response and 53% (18 of 35) for clinical remission.

Among the 74 patients who received extended induction, 70% (52 of 74) achieved clinical response and 53% (39 of 74) achieved clinical remission at week 8. By week 16, 69% (51 of 74) met criteria for clinical response and 55% (41 of 74) for clinical remission. By week 52, data was available for 55 of those 74 patients, 75% (41 of 55) met criteria for clinical response and 67% (37 of 55) for clinical remission.

When considering only those patients meeting criteria for clinical response at week 8 (70% of both cohorts), the standard induction cohort saw a 40% (14 of 35) loss of clinical response by week 16, with 46% (16 of 35) of these meeting criteria for clinical remission. In comparison, the extended induction cohort saw only 6% (3 of 52) loss of clinical response in

the same timeframe, with 73% (38 of 52) of these meeting criteria for clinical remission. In patients with clinical response at week 8, extended induction with 16 weeks of tofacitinib 10mg BD resulted in significantly improved maintenance of clinical response compared with standard induction (94% vs 60%, p=<0.01) and higher rates of clinical remission (73% vs 46%, p=<0.01).

These two cohorts were well matched in general, but the extended induction cohort had a significantly higher endoscopic disease severity at baseline (p=0.04) (Table 1). While there was no difference in the response rates between cohorts at week 8 (70% vs 70%, p = 0.48), a significant increase in the rate of clinical response for extended induction was seen at both week 16 (69% vs 46%, p = 0.02) and 52 (75% vs 54%, p = 0.03) compared to standard induction. Although clinical remission rates were also higher with extended induction, this difference did not reach statistical significance at week 16 (55% vs 44%, p = 0.25) or 52 (67% vs 53%, p = 0.22). (Figure 2). There were no significant predictors of response apart from duration of induction therapy when considering baseline clinical, biochemical and demographic status in either cohort.

The decision to pursue standard or extended induction was made entirely at the discretion of the treating physician, without any standardized criteria for deciding duration of induction considering baseline criteria or degree of response by week 8. As a result, we cannot deduce or comment if one cohort of patients may benefit most from an extended induction regime, or if this benefit extends to the entire cohort.

10.5. Other analyses

None.

10.6. Adverse events / adverse reactions

Over the 52 week follow up period, AEs were reported in 17% (21 of 124) of patients, collated in Table 3. The most common AEs were acne (5%), herpes zoster (5%) and nasopharyngitis (3%). No significant difference was seen in the rate of AE in those receiving standard vs extended induction (14% vs 18%, p=0.32), although over half (63%) of patients who experienced AEs occurred within the first 8 or 16 weeks while on the induction dose of 10mg BD and resolved after dose reduction. There were no reports of drug interruption or discontinuation due to AEs within the initial 8 or 16 week induction period, although 6 patients ultimately discontinued tofacitinib due to AEs, and were counted as SAEs.

SAEs were reported in 7% (9/124) of patients, with 6 requiring discontinuation of drug and 3 requiring hospital admission. The most common reason for drug discontinuation in these patients was recurrent herpes zoster infection (50%, 3/6), where the patients had not received shingles vaccine. Two required hospital admission for intravenous corticosteroid therapy due to ASUC, attributed to lack of efficacy rather than a drug related side-effect. The third admission was for the management of Clostridium difficile infection. During follow up, two patients underwent colectomy due to lack of response to tofacitinib. There was one case of non-melanomatous skin cancer (NMSC) reported, with no reported episodes of MACE, VTE, or malignancies.

11. DISCUSSION

11.1. Key results

A total of 124 patients (41% female; median age 41 [IQR 29-49] years) were identified, with 40% receiving standard induction and 60% receiving extended induction. Overall clinical response was achieved by 70% at week 8, 60% at week 16 and 68% at week 52. A significantly higher proportion of patients who received extended induction achieved clinical response by week 16 (69% vs 45%, p=0.02) and week 52 (75% vs 54%, p=0.03) compared with standard induction.

Clinical remission was achieved in 55% of the cohort at week 8, 52% at week 16 and 62% at week 52. No significant difference was observed in rate of clinical remission at any timepoint when stratified by duration of induction.

Adverse events were seen in 17% of patients over 52 weeks, consistent with previously published studies.

11.2. Limitations

This study has limitations inherent to its retrospective design, including the potential for recall bias which, although mitigated by the inclusion of all consecutively treated patients, is an unavoidable risk. The small cohort size and post-hoc nature of analysis may add further bias. Additionally, the limited availability of follow up endoscopic and biochemical data limited our ability to fully evaluate response durability. Variability in treatment practices across centres and clinician discretion in dosing and monitoring may also influence outcomes, making it challenging to directly generalize results across different healthcare settings.

11.3. Interpretation

Our findings confirm that tofacitinib is effective for induction of clinical response, clinical remission and CFCR in a real-world setting, with response rates higher than those reported in clinical trials.

11.4. Generalizability

None.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

In conclusion, tofacitinib is an effective and safe therapy in a real-world Australian population with moderate to severe ulcerative colitis, demonstrating high rates of clinical and corticosteroid free remission. Extended induction therapy with 10mg twice daily for 16 weeks resulted in higher clinical response rates observed at week 16, maintained through to week 52.

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15. LIST OF SOURCE TABLES AND FIGURES

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Document Approval Record

Document Name:	A3921405_Final Study Report_V1.0_29Sep2025
Document Title:	A3921405_Final Study Report_V1.0_29Sep2025

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