NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Comparative Effectiveness of Tofacitinib Versus Ustekinumab and Vedolizumab among Ulcerative Colitis Patients With Prior Anti- Tumor Necrosis Factor (TNF) Failure
Protocol number	A3921415
Version identifier of the final study report	1.0
Date	22 December 2022
EU Post Authorization Study (PAS) register number	EUPAS45035
Active substance	Tofacitinib citrate (ATC code L04AA29)
Research question and objectives	This retrospective matched cohort study will assess how tofacitinib, ustekinumab, and vedolizumab compare in real world safety and effectiveness of anti-TNF-experienced ulcerative colitis patients. Primary objectives: Compare proportions of corticosteroid-free clinical remission (Simple Clinical Colitis Activity Index [SCCAI] ≤2 or Mayo ≤2 or physician global assessment) in ulcerative colitis (UC) patients at 8-12 weeks and 52 weeks after tofacitinib, ustekinumab or vedolizumab initiation among patients with prior anti-TNF exposure.
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Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylate
AE	Adverse event
AEM	Adverse event monitoring
BMI	Body mass index
CRP	C-reactive protein
DCT	Data Collection Tools
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
IBD	Inflammatory bowel disease
ICD-10	International classification of Diseases, Tenth Revision
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
MGB	Mass General Brigham
NIS	Non-interventional study
PAS	Post-authorization study
PASS	Post-authorization safety study
PGA	Physician global assessment
RPDR	Research Patient Data Registry

Abbreviation	Definition
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard deviation
TNF	Tumor necrosis factor
UC	Ulcerative colitis
USA	United States of America
YRR	Your Reporting Responsibilities

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) Approval of Protocol	7 September 2021	NA	Protocol was exempt from IRB approval.
Start of Data Collection	01 March 2022	24 February 2022	
End of Data Collection	30 July 2022	27 July 2022	
Registration in the EU PAS Register	NA	28 February 2022	
Final Report of Study Results	30 June 2023	22 December 2022	

6. RATIONALE AND BACKGROUND

With limited head-to-head clinical trial data of advanced therapies in moderate-to-severe UC, the optimal relative positioning of tofacitinib, ustekinumab, and vedolizumab is unclear. A network meta-analysis of randomized trials determined that infliximab was the preferred first-line therapy for induction of remission in UC, followed by tofacitinib and ustekinumab after anti-Tumor Necrosis Factor (TNF) failure, and vedolizumab thereafter.[1] A more recent meta-analysis of clinical trials of biologics and small molecules for moderate-to-severe UC assessed upadacitinib, anti-TNF agents, vedolizumab, ustekinumab, ozanimod, and tofacitinib, among other therapies.[2] This study found vedolizumab to have the best safety profile with upadacitinib the best agent for induction of clinical remission. However, conclusions regarding the performance of tofacitinib relative to ustekinumab and vedolizumab were not made. As tofacitinib, ustekinumab, and vedolizumab therapy are commonly considered after failure of the anti-TNF class for UC, additional comparative data that reflect real-world outcomes are needed.

Our group recently conducted a real-world comparative effectiveness analysis of tofacitinib versus ustekinumab in vedolizumab and anti-TNF-exposed patients with UC was conducted, where no significant differences in corticosteroid-free clinical remission at 12-16 weeks were identified.[3] Similar comparisons for tofacitinib versus vedolizumab and longer-term outcomes with ustekinumab are needed to guide positioning of therapies, but data are currently lacking. Therefore the aim is to perform a retrospective matched cohort study to compare clinical outcomes up to 52 weeks after initiating these agents among anti-TNF exposed patients with UC in our health system.

This non-interventional study (NIS) is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer. The tofacitinib-treated patients in this protocol were derived from the same patient population in final study report A3921416.

7. RESEARCH QUESTION AND OBJECTIVES

This retrospective matched cohort study will assess how tofacitinib, ustekinumab and vedolizumab compare in real world safety and effectiveness of anti-TNF-experienced ulcerative colitis patients.

Primary objectives:

1. Compare proportions of corticosteroid-free clinical remission ((Simple Clinical Colitis Activity Index) SCCAI $\leq$2, if not available Mayo $\leq$2, if not available by physician global assessment [PGA] AND no use of oral or intravenous corticosteroids within 30 days of assessment) at 8-12 weeks after tofacitinib, ustekinumab, or vedolizumab initiation among patients with prior anti-TNF exposure.

2. Compare proportions of corticosteroid-free clinical remission at 52 weeks after tofacitinib, ustekinumab, or vedolizumab initiation among patients with prior anti-TNF exposure.

3. Compare drug survival (time to treatment discontinuation or colectomy) of tofacitinib versus ustekinumab and vedolizumab.

Secondary objectives:

1. Compare proportions of endoscopic response (ie, decrease in Mayo endoscopic subscore by 1 point) and endoscopic remission (Mayo endoscopic subscore =0) >8 weeks post-treatment initiation.

2. Assess proportions of biochemical response (improvement in C-reactive protein (CRP) or calprotectin by >25% or normalization) and remission (normalization of CRP or calprotectin) at first available assessment 8 weeks or later after drug initiation, among those with abnormal baseline values.

3. Compare proportions of colectomy, inflammatory bowel disease (IBD)-related hospitalization, and corticosteroid use within 52 weeks of treatment initiation.

4. Compare proportions of patient-reported improvement in articular extraintestinal manifestations within 52 weeks after treatment initiation.

5. Report proportions of potential complications (eg, infection, thromboembolism, shingles, new malignancy) during all available follow-up.

6. Describe reasons for treatment discontinuation.

8. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 substantial	21 March 2022	6. Milestones	Updated start of milestones to actual date	Administrative
		7. Rational and Background	Added ustekinumab as additional UC medication.	Since ustekinumab was added as a comparator arm it was also added to section 7 as an additional UC medication.
		8.Research questions and objectives	Primary objectives: Added ustekinumab as comparator, added a study objective to compare 52 weeks clinical remission ourcomes and deleted 8-12 weeks clinical response outcomes. Secondary objectives: Reduced the assessment of biochemical response to first available assessment 8 weeks after drug initiation.	Primary objectives: Changes were made to increase eligible study population/power of analysis, improve strength of analytical methods and to improve novelty of study with additional comparator. Secondary objectives: Several time points were collapsed into a broader, more inclusive time interval for biochemical response in order to maximize the total sample size for this outcome.
		9.1 Study Design	Changed the start date of time window to collect data from 01 October 2018 to 01 May 2018 and the end date from 01 January 2022 to 01 Apr 2022. Deletion the exclusion of patients previously exposed to other biologic classes. Addition of cohort specifications for vedolizumab and ustekinumab.	Changes were made in order to increase eligible study population and correspond to launch of tofacitinib in UC. The different treatment cohorts were clearer defined after review of existing data.
		9.2 Setting 9.2.1 Inclusion criteria	Changed the start date of time window to collect data from 01 October 2018 to 01 May 2018 and the end date from 01 January 2022 to 01 Apr 2022. Added ustekinumab as comparator.	Extension of time window to collect data in order to increase eligible study population and correspond to launch of tofacitinib in UC. Improve study novelty by adding ustekinumab as additional comparator.
		9.2.2 Exclusion criteria	Deletion of exclusion criteria of prior exposure to other biologics other than anti TNF agents.	Exclusion criteria was deleted to increase eligible study population

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		9.3 Variables	Added ustekinumab and corticosteroid free use within 30 days of outcome assessment to the list of variables. Deleted the histologic activity score.	In alignment with the addition of ustekinumab as comparator it was also added to the list of variables. Made definition of corticosteroid-free more specific/rigorous to be in line with previously published research and to provide a more clinically meaningful outcome. Our health system does not utilize a uniform histologic activity score in pathology reports.
		9.5 Study Size	Update of expected number of patients and ustekinumab cohort.	In coherence with the changes in patient selection (time window, addition of ustekinumab and exclusion criteria) the number of expected patients was updated.
		9.7 Data Analysis	Update of new cohort numbers in alignment with changes of study population. Modified data analysis to use propensity-scores instead of multivariable regression. Sample result tables were updated.	Changes in data analysis were made to improve the strength of analytical methods, as propensity scores can be used to balance confounders between treatment groups more effectively than multivariable logistic regression when the number of outcomes is small. Sample result tables were updated to be coherent with changes in the study protocol.
		9.9. Limitation of Research Methods	Addition of ustekinumab and deletion of multivariable logistic and Cox regression.	Changes were made to align with the addition of ustekinumab as comparator and the changes made in the data analysis section.
2 administrative	24 Aug 2022	6. Milestones	Updated milestones	Milestones were updated to align with sponsor internal system planned dates.
		Annex 1	Updated date of study abstract	Milestones were also updated in the study abstract, there for a new version of the abstract was created.

9. RESEARCH METHODS

9.1. Study Design

This was a retrospective cohort study of patients aged ≥18 years with UC who initiated tofacitinib, ustekinumab, or vedolizumab therapy on or after 01 May 2018 (month of tofacitinib US Food and Drug Administration [FDA] approval for UC) through 01 February 2022 in the Mass General Brigham (MGB) health system. Patient cohorts for research are identified using the MGB Research Patient Data Registry (RPDR), which filters Epic (the electronic health record of MGB) databases using specified search criteria including International Classification of Diseases, Tenth Revision (ICD-10) diagnoses, structured medication data, age, dates of interest, among other variables. RPDR then provides researchers with a list of medical record numbers, basic demographics, and specified variables of interest.

Only patients with prior anti-TNF alpha exposure were included. Because the cohort of vedolizumab-treated patients was expected to be more than 4 times the size of the cohort of tofacitinib-treated patients, 2:1 frequency matching by age (±3 years) and sex was performed to define the vedolizumab cohort using data automatically extracted from the RPDR. The ustekinumab cohort was anticipated to be similar in size to the tofacitinib cohort, therefore, all eligible ustekinumab-treated patients were included. Researchers performed manual chart review to collect other baseline independent variables, relevant confounders, and outcome data. Outcomes were assessed at clinic visits 8-12 weeks and 52 weeks after drug initiation. Drug survival was also assessed by following patients from the time of drug initiation to discontinuation due to loss of response (including colectomy due to loss of response). Patients were censored at total colectomy due to dysplasia/cancer or the last available gastroenterology encounter through 01 April 2022. Independent variables to be abstracted were baseline characteristics present at the time of drug initiation (or most recent available values within 3 months of initiation).

9.2. Setting

The study setting was the MGB health system, which includes Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Massachusetts General Hospital, Newton-Wellesley Hospital, McLean Hospital, and North Shore Medical Center in Massachusetts, United States of America (USA). Adult patients were included if they initiated tofacitinib, ustekinumab, or vedolizumab therapy for UC on or after 01 May 2018. Patient medical record numbers were identified using these search criteria in the MGB RPDR and thereafter Epic electronic health records were manually reviewed for clinical data. Patients were followed from the time of treatment initiation until treatment discontinuation, total colectomy, or the last available gastroenterology encounter through 01 April 2022.

9.3. Subjects

9.3.1. Inclusion Criteria

Subjects must have met all of the following inclusion criteria to be eligible for the study:

1. Age of 18 years or older.
2. Initiation of tofacitinib, ustekinumab, or vedolizumab therapy for ulcerative colitis on or after 01 May 2018 through 01 April 2022.
3. Prior anti-TNF exposure.
4. Patient within the MGB health system.

9.3.2. Exclusion Criteria

Subjects who met any of the following criteria were not included in the study:

1. History of prior colectomy.
2. Primary indication of tofacitinib, ustekinumab, or vedolizumab therapy is not ulcerative colitis.
3. Diagnosis of Crohn's disease or indeterminate colitis.
4. Dual therapy with tofacitinib and a biologic (eg, tofacitinib and vedolizumab or ustekinumab simultaneously) or vedolizumab/ustekinumab and a second biologic.

The tofacitinib-treated patients in this protocol were derived from the same patient population in final study report A3921416. Final patient populations may vary due to differences in inclusion/exclusion criteria.

9.4. Variables

Independent variables abstracted were baseline characteristics present at the time of tofacitinib, ustekinumab, or vedolizumab initiation (or most recent available values within 3 months of initiation). These included (but were not limited to):

Variable	Role	Data source(s)	Operational definition
Age	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
Sex	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
Race/ethnicity	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Demographics
Body mass index (BMI)	Baseline characteristic	Mass General Brigham Research Patient Data	Demographics

Variable	Role	Data source(s)	Operational definition
		Registry	
UC duration (years)	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Disease characteristics
Montreal disease extent	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Disease characteristics
Mayo endoscopic severity score (based on last colonoscopy)	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint
Mayo or SCCAI as documented in clinic notes	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Primary endpoint
Physician global assessment (PGA)	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Primary endpoint
Daily bowel movement frequency	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Disease characteristics
C-reactive protein	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint
Serum albumin	Baseline characteristic	Mass General Brigham Research Patient Data Registry	Confounder
Fecal calprotectin	Baseline characteristic/Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint
Concomitant and prior UC medications (corticosteroids, 5-ASA, azathioprine, 6-mercaptopurine, methotrexate, biologic or small molecule therapies)	Exposure	Mass General Brigham Research Patient Data Registry	Prior Concomitant medication
Oral or intravenous corticosteroid use within 30 days of outcome assessment	Outcome	Mass General Brigham Research Patient Data Registry	Primary endpoint
Substance use (current cannabis, current opioids)	Exposure, Baseline characteristics	Mass General Brigham Research Patient Data Registry	Demographics
Smoking (current, former, or never)	Exposure, Baseline characteristics	Mass General Brigham Research Patient Data Registry	Demographics
History of malignancy	Baseline characteristics	Mass General Brigham Research Patient Data Registry	Disease characteristics
UC-related hospitalization within the last 52 weeks	Baseline characteristics	Mass General Brigham Research Patient Data Registry	Disease characteristics
History of Colectomy (if applicable)	Baseline characteristics	Mass General Brigham Research Patient Data Registry	Disease characteristics
Extraintestinal manifestation (presence at drug initiation and improvement after drug	Baseline characteristics/Outcome	Mass General Brigham Research Patient Data Registry	Disease characteristics/secondary endpoint

Variable	Role	Data source(s)	Operational definition
initiation)			
Adverse events (AE)	Outcome	Mass General Brigham Research Patient Data Registry	Safety Data/secondary endpoint
Tofacitinib intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Mass General Brigham Research Patient Data Registry	NA
Ustekinumab intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Mass General Brigham Research Patient Data Registry	NA
Vedolizumab intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Mass General Brigham Research Patient Data Registry	NA
Reason for treatment discontinuation (primary/secondary loss of response, adverse event, colectomy for dysplasia)	Outcome	Mass General Brigham Research Patient Data Registry	Secondary endpoint

All independent variables were potential confounders and/or effect modifiers.

9.5. Data Sources and Measurement

The primary data source was Epic electronic health records and the majority of data was collected via manual chart review. Medical record numbers and demographic variables (sex, race/ethnicity) were obtained from the MGB RPDR using the pre-specified inclusion/exclusion criteria.

9.6. Bias

The study population includes referral patients at a tertiary center. Therefore, results may be biased towards individuals with more complex disease and may not reflect the general UC population in the United States. This is an inherent limitation to the study.

9.7. Study Size

The sample size that meets the inclusion/exclusion criteria was expected to be 70 patients in the tofacitinib group, 70 patients in the ustekinumab group, and 500 patients in the vedolizumab group per estimates from the RPDR. All eligible patients for the tofacitinib and ustekinumab comparison were to be included (ie, an estimated 140 patients). Two vedolizumab patients were to be frequency matched for every 1 tofacitinib patient by age and sex, resulting in a predicted final sample of approximately 210 patients for this comparison. Frequency matching was chosen due to time and resource limitations associated with manual review of 500 or more vedolizumab charts. Frequency matching was used to define the vedolizumab cohort in an unbiased fashion, but not for the sole purpose of controlling for confounding (to be addressed separately).

9.8. Data Transformation

Data were manually abstracted from Epic electronic medical records and collected using a Microsoft Excel template (this will serve as the Data Collection Tool), which were stored on a MGB computer and MGB Dropbox (cloud software). The excel file is password protected. No data transformations or calculations were performed beyond those described in the statistical methods (below).

9.9. Statistical Methods

De-identified data was imported into Stata/SE 17 for statistical analysis.

9.9.1. Main Summary Measures

Descriptive statistics were presented to describe patient characteristics. Categorical covariates were described by frequency distribution while continuous covariates were expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate. Continuous and categorical data were compared between treatment groups using the analysis of variance and generalized Fisher's exact test, respectively.

9.9.2. Main Statistical Methods

Statistical methods for tofacitinib vs ustekinumab

Propensity scores were estimated from a logistic regression model predicting tofacitinib vs ustekinumab treatment selection using the following covariates: age, female sex, UC duration, race, number of prior biologic exposures, current immunomodulator use, current prednisone or methylprednisolone use, last Mayo endoscopic subscore, last Montreal disease extent >E1, albumin, and BMI.

Inverse probability of treatment weighting (IPTW) was performed using propensity scores and covariate balance was assessed using absolute standardized differences between treatment groups.21 IPTW logistic and Cox regression were used to calculate adjusted odds ratios (aORs) and hazard ratios (aHRs) for the primary and secondary outcomes. For the Cox regression analysis, the proportional hazards assumption was tested using Schoenfeld residuals. Kaplan-Meier analysis with log-rank test was used to compare drug survival curves. Patients were censored at the time of colectomy for dysplasia, treatment discontinuation for reasons unrelated to non-response (eg, AEs or non-adherence), or at the last available gastroenterology encounter.

Statistical methods for tofacitinib vs vedolizumab

Univariable and multivariable logistic regression were used to calculated unadjusted and adjusted odds ratios (aORs) for the association of tofacitinib vs vedolizumab and SFCR at 8-12 weeks and 52 weeks. Multivariable analysis included the following baseline covariates chosen *a priori* (all binary unless specified): UC duration (continuous), number of prior anti-TNF exposures (continuous), albumin (continuous), immunomodulator use, oral/IV corticosteroid use, last MES=3, last Montreal disease extent >E1, and UC hospitalization within 12 months prior to drug initiation. Age and sex were not included because patients

were frequency matched on these characteristics. Because patients were frequency matched on only age and sex, unconditional logistic regression was chosen over conditional logistic regression for greater efficiency.

9.9.3. Missing Values

Patients with missing data for any independent variables were excluded from multivariable analyses.

9.9.4. Sensitivity Analyses

The study allowed for previous exposure to the comparator drug (eg, tofacitinib prior to ustekinumab or vice versa) if there was at least an 8-week washout period prior to inclusion in this study. However, this prior drug exposure may influence the probability of achieving remission with subsequent therapies. Therefore, a sensitivity analysis was performed that excluded patients with any prior exposure to tofacitinib or ustekinumab. This subpopulation was used to generate new IPTW logistic regression and Cox regression models.

9.9.5. Amendments to the Statistical Analysis Plan

For tofacitinib versus vedolizumab, IPTW and survival analyses were not performed due to the frequency matching study design and due to the fact that the majority of tofacitinib-treated patients were previously exposed to vedolizumab.

9.10. Quality Control

Data abstracted from electronic medical records were reviewed by 2 study investigators to ensure accuracy. The statistical analysis was completed by 1 study investigator and reviewed separately by a second investigator.

9.11. Protection of Human Subjects

Subject information and consent

Not applicable.

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

The study protocol was submitted to the IRB and received an exemption from IRB approval.

Ethical conduct of the study

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

10. RESULTS

10.1. Participants

The cohort for tofacitinib vs ustekinumab included 69 patients who initiated tofacitinib and 97 patients who initiated ustekinumab with a median follow-up of 88.0 weeks and 62.0 weeks, respectively.

The cohort for tofacitinib vs vedolizumab included 136 vedolizumab-treated patients who were frequency matched to 68 tofacitinib-treated patients. Median available follow-up was 89.9 weeks and 80.9 weeks for tofacitinib and vedolizumab, respectively.

10.2. Descriptive Data

For tofacitinib vs ustekinumab, baseline characteristics were similar except for immunomodulator use (9% tofacitinib vs 25% ustekinumab), Mayo endoscopic subscore of 2 or 3 (82% tofacitinib vs 69% ustekinumab), and CRP (median 5.1 mg/L tofacitinib vs 2.8 mg/L ustekinumab). Other baseline characteristics are presented in Table 1.

For tofacitinib vs vedolizumab, baseline characteristics were similar except patients in the tofacitinib group had more prior anti-TNF exposures (median 2 tofacitinib vs 1 vedolizumab) and had higher CRP (5.2 vs 3.2) and SCCAI scores (median 5 vs 3) compared to patients in the vedolizumab group. Other baseline characteristics are presented in Table 2.

Table 1. Baseline Characteristics for Tofacitinib vs Ustekinumab

Baseline Characteristics	Tofacitinib (n=69)	Ustekinumab (n=97)	P-value[†]
Female sex	42 (61%)	49 (51%)	0.19
Age, y, median (IQR)	41.2 (28.1, 54.0)	35.5 (29.4, 50.4)	0.25
UC duration, y, median (IQR)	9.5 (4.4, 15.5)	9.0 (4.1, 13.5)	0.39
Race			
Caucasian	63 (91%)	85 (88%)	0.40
Black	0 (0%)	4 (4%)	
Asian	4 (6%)	5 (5%)	
Other/Unknown	2 (3%)	3 (3%)	
Ethnicity			
Non-Hispanic	69 (100%)	89 (92%)	0.05
Hispanic	0 (0%)	4 (4%)	
Unknown	0 (0%)	4 (4%)	
Prior malignancy	4 (6%)	5 (5%)	0.86
Number of prior biologics, median (IQR)	2 (2,3)	2 (2,3)	0.62
Number of prior anti-TNFs, median (IQR)	2 (1,2)	1 (1,2)	0.18
Prior vedolizumab	51 (74%)	64 (66%)	0.27
Prior tofacitinib	0 (0%)	25 (26%)	n/a
Prior ustekinumab	8 (12%)	0 (0%)	n/a
Prior 5-ASA	67 (97%)	94 (97%)	0.94
Current 5-ASA	10 (14%)	19 (20%)	0.39
Prior immunomodulator	54 (78%)	70 (72%)	0.37
Current immunomodulator	6 (9%)	24 (25%)	0.008
Current Oral/IV corticosteroids			0.41

Baseline Characteristics	Tofacitinib (n=69)	Ustekinumab (n=97)	P-value[†]
Prednisone/Methylprednisolone	30 (43%)	51 (53%)	
Budesonide	7 (10%)	11 (11%)	
BMI, kg/m2, median (IQR)	25.79 (21.8, 28.9)	25.1 (21.7, 29.0)	0.97
Arthralgia at time of drug initiation	26 (38%)	26 (27%)	0.14
Last Montreal disease extent >E1 (ie >proctitis)[‡]	59 (86%)	75 (77%)	0.19
Last Mayo endoscopic subscore (severity)[‡]			0.049
0 (None)	6 (9%)	10 (10%)	
1 (Mild)	7 (10%)	20 (21%)	
2 (Moderate)	37 (54%)	32 (33%)	
3 (Severe)	19 (28%)	35 (36%)	
Smoking			0.31
Never	56 (81%)	70 (72%)	
Current	2 (3%)	2 (2%)	
Former	11 (16%)	25 (26%)	
Current cannabis use	9 (13%)	22 (23%)	0.12
Current opioid use	6 (9%)	3 (3%)	0.12
UC hospitalization within 12 months	18 (26%)	21 (22%)	0.51
Serum albumin, g/dL, median (IQR)	4.1 (3.8, 4.3)	4.1 (3.8, 4.4)	0.47
C-reactive protein, mg/L, median (IQR)	5.1 (1.8, 22.8)	2.8 (1, 7)	0.01
Fecal calprotectin > 120 ug/g	25 (89%)	49 (88%)	0.81
SCCAI, median (IQR)	5 (4, 8)	5 (3, 7)	0.46
Daily bowel movement frequency, median (IQR)	6 (4, 10)	6 (4, 9)	0.57

[†]Calculated using Pearson's chi squared and Wilcoxon rank-sum tests.
[‡]Median time from endoscopic evaluation to drug initiation was 19.1 weeks (IQR 6.1-46.1 weeks) for tofacitinib and 22.4 weeks (IQR 3.9 -44.1 weeks) for ustekinumab.
Abbreviations: IQR = interquartile range, TNF= tumor necrosis factor, ASA = aminosalicylic acid, SCCAI = simple clinical colitis activity index.

Table 2. Baseline Characteristics for Tofacitinib vs Vedolizumab

Baseline Characteristic	Tofacitinib (n=68)	Vedolizumab (n=136)	P-value[a]
Female	42 (61.8%)	84 (61.8%)	1.00
Age, y, median (IQR)	41.7 (28.1, 55.0)	42.0 (30.3, 54.2)	0.90
UC duration, y, median (IQR)	9.8 (4.4, 16.0)	10.1 (4.6, 16.1)	0.99
Race			0.87
Caucasian	62 (91.2%)	125 (91.9%)	
Black	0 (0.0%)	1 (0.7%)	
Asian	4 (5.9%)	6 (4.4%)	
Other/Unknown	2 (2.9%)	4 (2.9%)	
Hispanic	0 (0.0%)	4 (2.9%)	0.15
Malignancy history	4 (5.9%)	15 (11.0%)	0.23
Number of prior anti-TNFs, median (IQR)	2 (1, 2)	1 (1, 2)	<0.01
Prior vedolizumab	50 (73.5%)	0 (0.0%)	<0.01[b]
Prior tofacitinib	0 (0.0%)	2 (1.5%)	0.31[b]
Prior ustekinumab	8 (11.8%)	1 (0.7%)	<0.01
Prior 5-ASA	66 (97.1%)	136 (100.0%)	0.04
Current 5-ASA	10 (14.7%)	44 (32.4%)	0.01
Prior immunomodulator	54 (79.4%)	74 (54.4%)	<0.01

Baseline Characteristic	Tofacitinib (n=68)	Vedolizumab (n=136)	P-value[a]
Current immunomodulator	6 (8.8%)	32 (23.5%)	0.01
Current Oral/IV corticosteroids	36 (52.9%)	84 (61.8%)	0.23
BMI, kg/m2 median (IQR)	25.9 (21.9, 29.0)	25.8 (22.5, 29.5)	0.47
Articular manifestations	26 (38.2%)	24 (17.6%)	0.00
Montreal disease extent >E1 (proctitis)	58 (85.3%)	113 (83.1%)	0.69
Mayo endoscopic severity			0.05
0 (None)	6 (8.8%)	11 (8.1%)	
1 (Mild)	7 (10.3%)	35 (25.7%)	
2 (Moderate)	36 (52.9%)	51 (37.5%)	
3 (Severe)	19 (27.9%)	39 (28.7%)	
Smoking			0.30
Never	55 (80.9%)	95 (69.8%)	
Current	2 (2.9%)	4 (2.9%)	
Former	11 (16.2%)	37 (27.2%)	
Current cannabis use	9 (13.2%)	19 (14.0%)	0.89
Current opioid use	6 (8.8%)	2 (1.5%)	0.01
UC hospitalization within 12 months	17 (25.0%)	34 (25.0%)	1.00
Serum albumin, g/dL, median (IQR)	4.1 (3.8, 4.3)	4.1 (3.8, 4.4)	0.91
C-reactive protein, mg/L, median (IQR)	5.2 (1.8, 22.8)	3.15 (1.1, 10.8)	0.02
Fecal calprotectin >120 ug/g	25 (89%)	63 (83%)	0.42
SCCAI, median (IQR)	5 (4, 8)	3 (2, 5)	<0.01
Daily bowel movement frequency, median (IQR)	6 (3.5, 10)	4 (2, 6.5)	<0.01

a. P-values calculated using Fisher's exact test or Wilcoxon rank-sum test.

b. If a patient's last treatment was vedolizumab or tofacitinib, there was a washout period of ≥8 weeks prior to initiating the next treatment.

Abbreviations: IQR = interquartile range, TNF= tumor necrosis factor, ASA = aminosalicylic acid, SCCAI = simple clinical colitis activity index.

10.3. Outcome Data

Tofacitinib vs ustekinumab outcomes

At 12 weeks, 53% (36/68) of tofacitinib patients and 32% (31/96) of ustekinumab patients were in SFCR (p<0.01). At 52 weeks, 56% (37/66) of tofacitinib patients and 49% (44/90) of ustekinumab patients were in SFCR (p=0.38) (Figure 1). During all available follow-up time (see Section 10.1), treatment was discontinued among 43% (30/69) of tofacitinib patients and 39% (38/97) of ustekinumab patients. Documented reasons for treatment discontinuation included non-response (83% tofacitinib, 90% ustekinumab), colectomy for dysplasia (7% tofacitinib, 8% ustekinumab), AEs (3% tofacitinib, 3% ustekinumab), insurance coverage (3% tofacitinib, 0% ustekinumab), and self-discontinuation (3% tofacitinib, 0% ustekinumab).

Within 52 weeks, 71% (20/28) of tofacitinib patients and 61% (19/31) of ustekinumab patients had endoscopic response (p=0.41), 25% (7/28) and 13% (4/31) had endoscopic remission (p=0.23), 55% (12/22) and 58% (11/19) had improvement in arthralgia (p=0.83), 75% (21/28) and 80% (28/35) had biochemical response (p=0.64), 61% (17/28) and 54% (19/35) had biochemical remission (p=0.61), 2% (1/45) and 9% (5/55) had UC-related hospitalization (p=0.22), 14% (7/50) and 12% (8/67) had colectomy due to refractory disease (p=0.78), and 30% (20/66) and 29% (27/93) discontinued treatments due to non-response (p=0.87). Hospitalization and colectomy outcomes only included patients who remained on treatment for the full duration of 52 weeks unless the outcome occurred prior to 52 weeks (Figure 1).

During all available follow-up time, 35/66 tofacitinib patients who were initially started on 10 mg twice daily dosing were de-escalated to 5 mg twice daily (32/35) or 10 mg / 5 mg twice daily (ie, 15 mg total daily; 3/35). For ustekinumab, 43/97 were dose escalated to every 4-week and 16/97 were dose escalated to every 6-week dosing.

Tofacitinib vs vedolizumab outcomes

Due to missing data or insufficient follow-up, cohort sizes vary by outcome. At 12 weeks, 54% (36/67) of tofacitinib patients and 46% (62/136) of vedolizumab patients were in SFCR (p=0.27). At 52 weeks, 59% (37/63) of tofacitinib patients and 45% (57/128) of vedolizumab patients were in SFCR (p=0.07).

Within 52 weeks, 74% (20/27) of tofacitinib patients and 55% (35/64) of vedolizumab patients had endoscopic response (p=0.08), 30% (8/27) and 27% (17/64) had endoscopic remission (p=0.76), 55% (12/22) and 50% (11/22) had improvement in arthralgia (p=0.83), 71% (7/24) and 59% (26/44) had biochemical response (p=0.34), and 46% (11/23) and 32% (14/44) had biochemical remission (p=0.25). Additionally, 6% (4/68) of tofacitinib patients and 9% (17/136) of vedolizumab patients had UC hospitalization (p=0.14), 30% (19/64) and 30% (36/120) discontinued treatment due to non-response (p=0.87), and 2% (3/136) and 0% (0/68) discontinued treatment due to an AE (p=0.55) within 52 weeks (Figure 2).

During all available follow-up time, 35/66 patients who started tofacitinib 10 mg twice daily were dose de-escalated to 5 mg twice daily or 10 mg and 5 mg twice daily (15 mg total) dosing. For vedolizumab, 43/136 patients were dose escalated to every 4-week dosing and 22/136 were dose escalated to every 6-week dosing.

Figure 1. Unadjusted Outcomes for Tofacitinib vs Ustekinumab

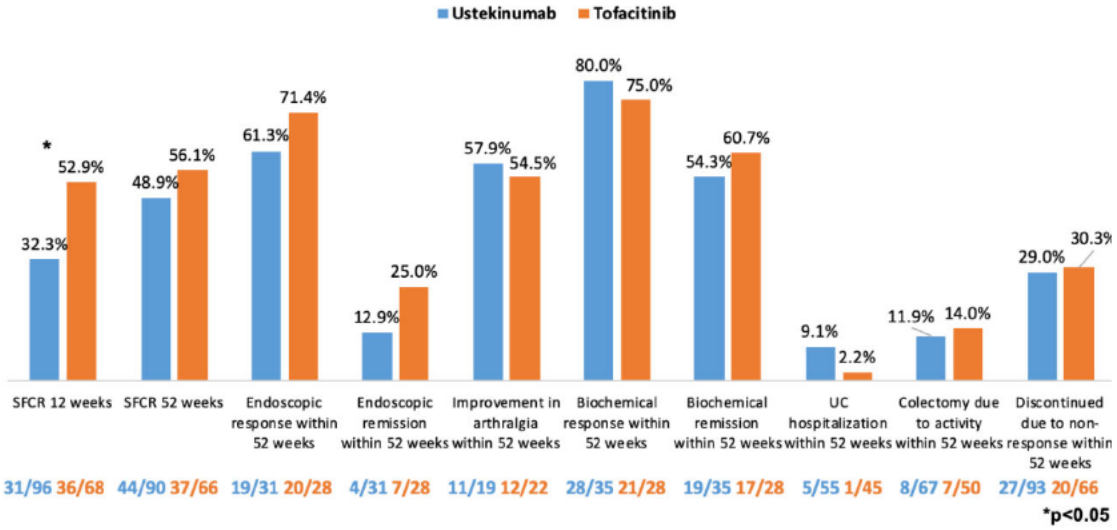
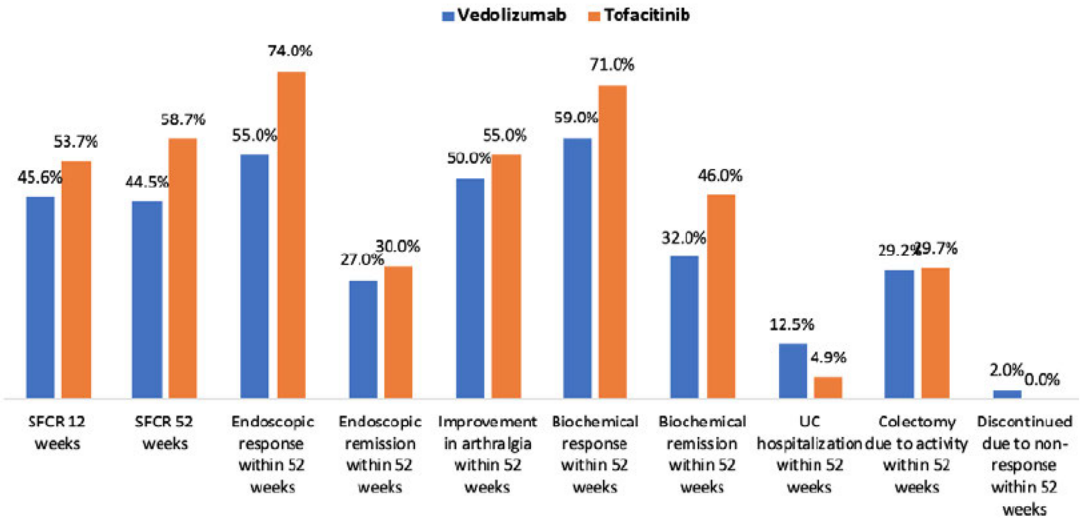


Figure 2. Unadjusted Outcomes for Tofacitinib vs Vedolizumab



Vedolizumab n/N:	62/138	57/128	35/64	17/64	11/22	26/44	14/44	17/136	36/120	2/136
Tofacitinib n/N:	36/67	37/63	20/27	8/27	12/22	17/24	11/24	4/68	19/64	0/68

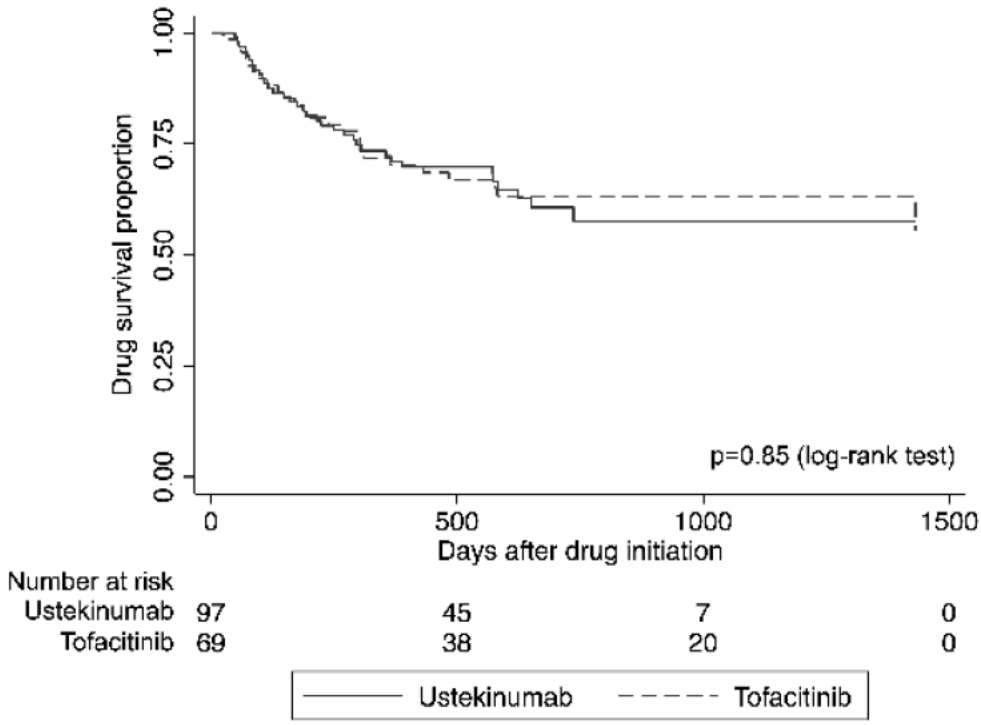
10.4. Main Results

Tofacitinib vs ustekinumab main results

After IPTW, covariate balance between treatment groups was confirmed with <10% absolute standardized differences. In the unweighted logistic regression models, there was a significantly higher odds of SFCR at 12 weeks for tofacitinib vs ustekinumab (OR 2.36, 95% CI 1.24-4.47) but no significant difference for SFCR at 52 weeks (OR 1.33, 95% CI 0.70-2.52). After IPTW, there were no significant differences in SFCR at 12 weeks (OR 1.94, 95% CI 0.96-3.2) or 52 weeks (OR 1.16, 95% CI 0.58-2.31) for tofacitinib vs ustekinumab.

Kaplan-Meier analysis demonstrated no separation in the drug survival curves related to non-response for tofacitinib and ustekinumab (Figure 3). The unweighted Cox model showed no significant difference in drug survival related to non-response for tofacitinib vs ustekinumab (HR 0.95, 95% CI 0.57-1.60). Results were similar after IPTW (aHR 1.26, 95% CI 0.74-2.15). The proportional hazards assumption was confirmed using Schoenfeld residuals.

Figure 3. Kaplan-Meier Analysis of Tofacitinib and Ustekinumab Drug Survival Due to Non-Response



Tofacitinib vs vedolizumab main results

In the univariable logistic regression models, there was no association between tofacitinib vs vedolizumab with SFCR at 12 weeks (OR 1.39, 95% CI 0.77-2.49) or 52 weeks (1.77, 95% CI 0.96-3.26). After multivariable analysis, there was no association between tofacitinib vs vedolizumab with SFCR at 12 weeks (aOR 1.45, 95% CI 0.76-2.77) but tofacitinib was associated with a significantly higher odds of SFCR at 52 weeks (aOR 2.11, 95% CI 1.05-4.23).

10.5. Other Analyses

In the sensitivity analysis that excluded patients with prior exposure to tofacitinib or ustekinumab, the sample size was reduced to 133 patients (n=61 tofacitinib, 72 ustekinumab). After IPTW, there were no significant differences in the primary and secondary outcomes for tofacitinib vs ustekinumab: SFCR 12 weeks (aOR 1.35, 95% CI 0.61-2.98), SFCR 52 weeks (aOR 1.21, 9 5% CI 0.54-2.73), and drug survival (aHR 1.09, 95% CI 0.58-2.06).

10.6. Adverse Events/Adverse Reactions

During available follow-up, there was 1 AE attributed to tofacitinib therapy, which was elevated liver enzymes. This patient discontinued tofacitinib due to the AE. There were also 2 reported "possible miscarriages," one of which was associated with a positive beta HCG followed by a negative beta HCG 3 days later. The second involved a patient who reported observation of a miscarriage but there was no laboratory or other objective documentation to confirm pregnancy. Neither patient intended to become pregnant and neither discontinued tofacitinib due to these events. Of note, these patients were derived from the same patient population in final study report A3921416.

One AE was attributed to ustekinumab therapy, which was arthralgia. This patient discontinued ustekinumab due to the AE.

Two AEs were attributed to vedolizumab therapy, which were perforated diverticulitis and nausea with oral pain. These patients discontinued vedolizumab due to these AEs.

11. DISCUSSION

11.1. Key Results

Tofacitinib vs ustekinumab

At 52 weeks, approximately 50% of patients in both treatment groups achieved SFCR. There were also high proportions (>60%) of patients in both treatment groups who had endoscopic response within 52 weeks. After adjustment for confounders, there we no differences in the odds of achieving SFCR at either 12 or 52 weeks. There were no differences in drug survival related to non-response between tofacitinib and ustekinumab. In the sensitivity analysis of tofacitinib and ustekinumab-naïve patients, these adjusted results were unchanged.

Tofacitinib vs vedolizumab

At 52 weeks, >45% of patients in each treatment group achieved SFCR. After adjusting for confounders, tofacitinib was associated with higher odds of SFCR at 52 weeks. AEs leading to discontinuation within 52 weeks were rare, and no deaths occurred during follow-up.

11.2. Limitations

Limitations include the retrospective nature of this study allowed for missing or incomplete outcome data, non-standardized reporting of potential AEs, and the inability to detect clinical events that may have occurred outside of our health system. Our primary outcomes relied on documentation of SCCAI scores or subjective provider assessments of clinical remission, which may suffer from inter-provider variability. We therefore included an assessment of drug survival related to clinical response, which may be a more objective measure of drug performance. While we have expanded our cohort size from a prior study comparing tofacitinib to ustekinumab, there is still insufficient power to detect small differences in outcomes for which larger studies are needed. Similarly, this observational study was not designed to detect differences in endoscopic outcomes, as the decision to undergo endoscopy post-drug initiation was not standardized. A prospective study design would be needed for this purpose.

There may also be residual confounding from unmeasured variables that may influence outcomes. Finally, the main analysis for tofacitinib vs ustekinumab included patients with prior exposure to tofacitinib and ustekinumab, which may influence the likelihood of response to subsequent therapies. However, results for SFCR outcomes were unchanged after these patients were excluded. In the analysis of tofacitinib vs vedolizumab, most tofacitinib patients were previously exposed to vedolizumab. This may differentially effect the likelihood of response to future therapies. However, we suspect that any bias related to prior vedolizumab exposure would decrease the chance of type I error.

11.3. Interpretation

Tofacitinib vs ustekinumab

Treatment selection after anti-TNF failure is a commonly encountered challenge in clinical practice that merits further research. To our knowledge, we have presented the largest real-world study to-date that directly compares the effectiveness of tofacitinib to ustekinumab at 52 weeks among patients with UC and prior anti-TNF failure.

Before adjustment for confounders, we observed that 53% of patients receiving tofacitinib and 32% of patients receiving ustekinumab achieved SFCR at 12 weeks, though patients in the tofacitinib group had higher baseline Mayo endoscopic subscores and CRP. At 52 weeks, approximately 50% of patients in both treatment groups achieved SFCR. There were also high proportions (>60%) of patients in both treatment groups who had endoscopic response within 52 weeks. After adjustment for confounders, there we no differences in the odds of achieving SFCR at either 12 or 52 weeks. Additionally, there were no differences in drug survival related to non-response between tofacitinib and ustekinumab. In the sensitivity

analysis of tofacitinib and ustekinumab-naïve patients, these adjusted results were unchanged.

Both drugs were well-tolerated, as only one patient in each treatment group discontinued therapy due to an AE during >260 patient-years of follow-up. While the absolute number of AEs during available follow-up were higher in the tofacitinib vs ustekinumab group (17 vs 10), tofacitinib patients had longer available follow-up time (median of 88 vs 62 weeks) which limits comparisons. Additionally, real-world documentation of potential AEs is likely to be heterogenous between providers and attribution of AEs to therapy is often subjective. Therefore AEs leading to treatment discontinuation are likely the most clinically meaningful in this retrospective analysis.

While the study did not identify a significant difference in the adjusted odds of SFCR at 12 weeks, there was an absolute difference with OR 1.94 (p=0.06) favoring tofacitinib. This may be the result of type II error, and larger studies may identify a significantly higher odds of remission at early time points with tofacitinib compared to ustekinumab. Such findings would be consistent with the known rapid onset of action of tofacitinib, and this may be an important consideration when a fast therapeutic effect is prioritized.

This study has several strengths. We utilized propensity scores to adjust for potential confounding by indication for tofacitinib vs ustekinumab. After IPTW, baseline covariates between treatment groups were successfully balanced, simulating the design of a randomized trial. The study also provided granular clinical data including endoscopic and biochemical results, dose optimizations, AEs, and documented reasons for treatment discontinuation during follow-up, which have not been previously compared. Despite the inherent limitations of observational research, this study provides an important perspective of real-world clinical practice that is not subject to the stringent inclusion and exclusion criteria of RCTs.

Tofacitinib vs vedolizumab

To our knowledge, this is the first real-world cohort study in the United States to directly compare 52 week outcomes of tofacitinib to vedolizumab among patients with UC and prior anti-TNF failure. We observed that both therapies were effective for this population, with >45% of patients in both treatment groups achieving SFCR at 12 and 52 weeks and >50% achieving endoscopic response within 52 weeks. After adjusting for confounders related to disease severity, tofacitinib was associated with significantly higher odds of both SFCR at 52 weeks. There were no differences in treatment discontinuation due to non-response within 52 weeks, and AEs that led to treatment discontinuation were uncommon in both groups.

This study has several strengths. We had complete cohort data for several variables reflecting baseline disease activity, including recent hospitalizations, serum markers, and endoscopic data, all of which were included in our multivariable analyses. Our use of frequency matching created nearly identical age and sex distributions between treatment groups. This study provides important comparative data regarding both clinical and endoscopic outcomes of tofacitinib and vedolizumab in a real-world cohort in the United States.

11.4. Generalizability

The study was conducted in an urban, tertiary referral center. The majority of patients were also Caucasian. Therefore the results of this study may not be generalizable to other settings and populations of different demographic compositions.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In this study, which extends upon the data of tofacitinib-treated patients from protocol A3921416, tofacitinib was associated with higher odds of SFCR at 52 weeks compared to vedolizumab and similar odds of SFCR at 52 weeks compared to ustekinumab. AEs were consistent with known safety profiles of these therapies. These data support the use of tofacitinib among patients with UC and prior anti-TNF failure. Prospective studies are needed to verify these findings and compare other important outcomes, such as mucosal and histologic healing.

14. REFERENCES

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15. LIST OF SOURCE TABLES AND FIGURES

All tables and figures are included in the body of the study report.

Document Approval Record

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