NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Comparative Effectiveness of Tofacitinib Versus Ustekinumab and Vedolizumab among Ulcerative Colitis (UC) Patients With Prior Anti- Tumor Necrosis Factor (TNF) Failure
Protocol number	A3921415
Protocol version identifier	2.0
Date	08 April 2022
EU Post Authorization Study (PAS) register number	EUPAS45035
Active substance	Tofacitinib citrate
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 UC patients. Primary objectives: Compare proportions of corticosteroid-free clinical remission (Simple Clinical Colitis Activity Index (SCCAI) <2 or Mayo <2 or physician global assessment (PGA)) in 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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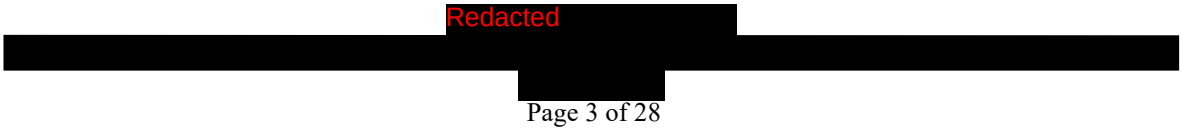

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylate
AE	adverse event
AEM	adverse event monitoring
AIBD	Advances in Inflammatory Bowel Diseases
BMI	body mass index
CRP	C-reactive protein
DCT	data collection tools
DDW	Digestive Disease Week
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
IPTW	inverse probability of treatment weighting
IQR	interquartile range
IRB	Institutional Review Board
MGB	Mass General Brigham
NIS	non-interventional study
PAS	post-authorization study

Abbreviation	Definition
PASS	post-authorization safety study
PGA	physician global assessment
RPDR	research patient data registry
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. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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Redacted	[redacted]	[redacted]	[redacted]5

4. ABSTRACT

Stand-alone document. Please see ANNEX 1.

5. 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 and additional UC medication.
		8. Research questions and objectives	Primary objectives: Added ustekinumab as comparator, added a study objective to compare 12 months 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 April 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 April 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.

6. MILESTONES

Milestone	Planned date
Start of data collection	24 February 2022
End of data collection	30 May 2022
Registration in the European Union (EU) PAS register	23 February 2022
Final study report	30 March 2023

7. 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- 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 12 months 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.

8. 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 UC patients.

Primary objectives:

1. Compare proportions of corticosteroid-free clinical remission (SCCAI $\leq$2, if not available Mayo $\leq$2, if not available by 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 <1) >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 intiation.
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.

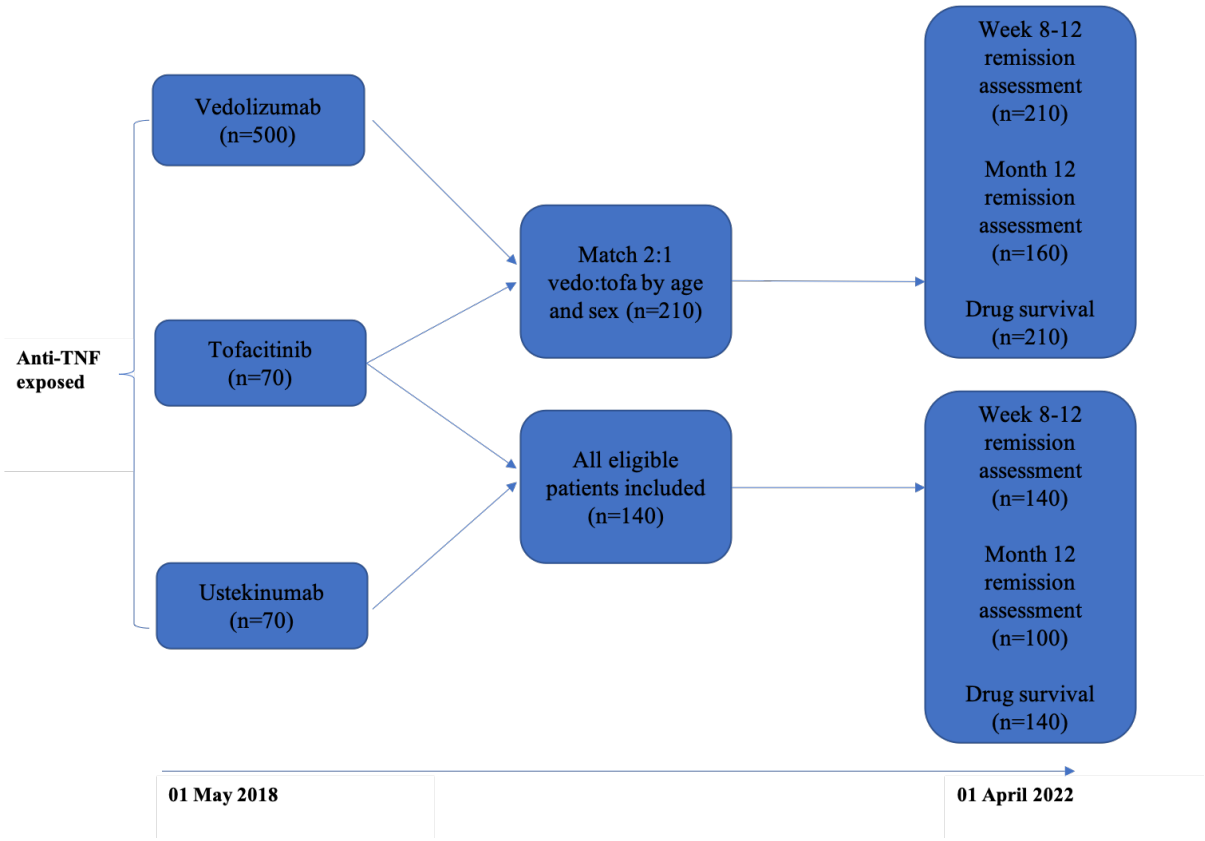
9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study of patients aged ≥18 years with UC who initiate 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 will be included. Because the cohort of vedolizumab-treated patients is 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 will be used to define the vedolizumab cohort using data automatically extracted from the RPDR. The ustekinumab cohort is anticipated to be similar in size to the tofacitinib cohort, therefore, all eligible ustekinumab-treated patients will be included. Researchers will then perform manual chart review to collect other baseline independent variables, relevant confounders, and outcome data. Outcomes will be assessed at clinic visits 8-12 weeks and 12 months after drug initiation. Drug survival will also be 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 will be censored at total colectomy due to dysplasia/cancer or the last available gastroenterology encounter through 01 April 2022 (Figure 1). Independent variables to be abstracted are baseline characteristics present at the time of drug initiation (or most recent available values within 3 months of initiation).

Figure 1. Study Design



All n's are estimates. Final sample sizes may vary slightly after detailed chart review.

9.2. Setting

The study setting is the MGB health system, which includes Redacted [redacted] Adult patients will be included if they initiated tofacitinib, ustekinumab, or vedolizumab therapy for UC on or after 01 May 2018. Patient medical record numbers will be identified using these search criteria in the MGB RPDR and thereafter Epic electronic health records will be manually reviewed for clinical data. Patients will be followed from the time of treatment initiation until treatment discontinuation, total colectomy, or the last available gastroenterology encounter through 01 April 2022.

9.2.1. Inclusion Criteria

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

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

9.2.2. Exclusion Criteria

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

1. History of prior colectomy.
2. Primary indication of tofacitinib, ustekinumab, or vedolizumab therapy is not UC.
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.

9.3. Variables

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

Variable	Role	Data source(s)	Operational definition
Age	Baseline characteristic	MGB RPDR	Demographics
Sex	Baseline characteristic	MGB RPDR	Demographics
Race/ethnicity	Baseline characteristic	MGB RPDR	Demographics
Body mass index (BMI)	Baseline characteristic	MGB RPDR	Demographics
UC duration (years)	Baseline characteristic	MGB RPDR	Disease characteristics
Montreal disease extent	Baseline characteristic	MGB RPDR	Disease characteristics
Mayo endoscopic severity score (based on last colonoscopy)	Baseline characteristic/Outcome	MGB RPDR	Secondary endpoint

Variable	Role	Data source(s)	Operational definition
Mayo or SCCAI as documented in clinic notes	Baseline characteristic/Outcome	MGB RPDR	Primary endpoint
PGA	Baseline characteristic/Outcome	MGB RPDR	Primary endpoint
Daily bowel movement frequency	Baseline characteristic/Outcome	MGB RPDR	Disease characteristics
CRP	Baseline characteristic/Outcome	MGB RPDR	Secondary endpoint
Serum albumin	Baseline characteristic	MGB RPDR	Confounder
Fecal calprotectin	Baseline characteristic/Outcome	MGB RPDR	Secondary endpoint
Concomitant and prior UC medications (corticosteroids, 5-aminosalicylate [5-ASA], azathioprine, 6-mercaptopurine, methotrexate, biologic or small molecule therapies)	Exposure	MGB RPDR	Prior Concomitant medication
Oral or intravenous corticosteroid use within 30 days of outcome assessment	Outcome	MGB RPDR	Primary endpoint
Substance use (current cannabis, current opioids)	Exposure, Baseline characteristics	MGB RPDR	Demographics
Smoking (current, former, or never)	Exposure, Baseline characteristics	MGB RPDR	Demographics
History of malignancy	Baseline characteristics	MGB RPDR	Disease characteristics
UC-related hospitalization within the last 12 months	Baseline characteristics	MGB RPDR	Disease characteristics
History of Colectomy (if applicable)	Baseline characteristics	MGB RPDR	Disease characteristics
Extraintestinal manifestation (presence at drug initiation and improvement after drug initiation)	Baseline characteristics/Outcome	MGB RPDR	Disease characteristics/secondary endpoint
Adverse events (AE)	Outcome	MGB RPDR	Safety Data/secondary endpoint
Tofacitinib intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	MGB RPDR	NA
Ustekinumab intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	MGB RPDR	NA
Vedolizumab intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	MGB RPDR	NA

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Variable	Role	Data source(s)	Operational definition
Reason for treatment discontinuation (primary/secondary loss of response, AE, colectomy for dysplasia)	Outcome	MGB RPDR	Secondary endpoint

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

9.4. Data Sources

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

9.5. Study Size

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

All n's are estimates. Final sample sizes may vary slightly after detailed chart review.

9.6. Data Management

Data will be manually abstracted from Epic electronic medical records and collected using a Microsoft Excel template (this will serve as the Data Collection Tool), which will be stored on a MGB computer and MGB Dropbox (cloud software). The excel file will be *password protected*.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

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

A DCT is required and should be completed for each included patient. The completed original DCTs 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. MGB shall ensure that the DCTs are securely stored at the MGB in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

MGB has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs must be signed by the researcher or by an authorized staff member to attest that the data contained on the DCTs are true. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, MGB agrees to keep all study-related records, including sufficient information to link records, DCTs and hospital records, 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 MGB according to local regulations or as specified in the research agreement, whichever is longer. MGB must ensure that the records continue to be stored securely for so long as they are retained.

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

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

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

9.7. Data Analysis

After patient cohorts are identified in the MGB RPDR using the pre-specified inclusion and exclusion criteria, vedolizumab patients will be frequency matched 2:1 to tofacitinib patients by age (±3 years) and sex. The matched sample will be used for all subsequent analyses for this comparison. All eligible ustekinumab patients will be used in the tofacitinib vs ustekinumab comparison. De-identified data will be imported into StataSE 17 for statistical analysis.

The sample size that meets the inclusion/exclusion criteria is 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. Because there are several hundred more vedolizumab-treated patients with UC within our health system compared to tofacitinib-treated patients, 2 vedolizumab patients will be frequency matched for every 1 tofacitinib patient by age and sex, resulting in a final sample of approximately 210 patients. Assuming proportions of corticosteroid free clinical remission to range between 0.30 and 0.55 (based on prior data), the study will have a maximum power of 0.92 (tofacitinib vs vedolizumab) and 0.81 (tofacitinib vs ustekinumab) to detect a 0.25 difference in outcomes.

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

Two propensity scores will be calculated using a logistic regression model to predict treatment of tofacitinib versus ustekinumab and tofacitinib versus vedolizumab using the following *a priori* covariates (ie, confounders): age, sex, race, last Mayo endoscopic subscore, disease extent, serum albumin, disease duration, current corticosteroid use, current immunomodulator use, number of prior biologic or small molecule therapies, and UC hospitalization within the prior 12 months.

The propensity scores will then be used to calculate inverse probability of treatment weights for each comparison. Inverse probability of treatment weighting (IPTW) will serve as the primary method to adjust for confounding and treatment selection bias. The IPTW samples will then be utilized in two logistic regression models determining the association between tofacitinib versus ustekinumab and vedolizumab therapy on remission at 8-12 weeks and 12 months.

A survival analysis of time to treatment discontinuation or colectomy due to non-response will also be conducted. First, two unweighted Kaplan-Meier analyses with log-rank test stratified by treatment will be performed. Subsequently, two IPTW Cox proportional hazards models will be built to determine the association of tofacitinib versus ustekinumab and vedolizumab therapy with time to treatment discontinuation or colectomy due to non-response.

Patients with missing data for any independent variables will be excluded from these logistic regression and survival analyses. If there is sufficient data, subgroup analyses for patients with only one prior anti-TNF failure and those with multiple prior anti-TNF failures will also be considered.

Sample result tables are included below.

Table 1. Baseline Characteristics: Tofacitinib versus Ustekinumab

Characteristics	Tofacitinib	Ustekinumab	P-value
Female, fraction (%)			
Age, y, mean (SD)			
UC duration, y, mean (SD)			
BMI, mean (SD)			
Race, fraction (%)			
White			
Black			
Asian			
Disease extent, fraction (%)			
Proctitis only			
More extensive than proctitis			
Last Mayo endoscopic subscore, fraction (%)			
Normal or mild (≤1)			
Moderate (2)			
Severe (3)			
Extraintestinal manifestation, fraction (%)			
1 prior anti-TNF, fraction (%)			
>1 prior anti-TNF, fraction (%)			
Number of prior biologic or small molecule exposures, median (IQR)			
Prior immunomodulator, fraction (%)			
Current immunomodulator, fraction (%)			
Current corticosteroids, fraction (%)			
Current smoking, fraction (%)			
Current cannabis, fraction (%)			
Current opioids, fraction (%)			
SCCAI, mean (SD)			
Laboratory values			
Serum Albumin, mean (SD), g/dL			
CRP, mean (SD), mg/L			
Fecal calprotectin, median (IQR), µg/g			

Table 2. Baseline Characteristics: Tofacitinib versus Vedolizumab

Characteristics	Tofacitinib	Vedolizumab	P-value
Female, fraction (%)			
Age, y, mean (SD)			
UC duration, y, mean (SD)			
BMI, mean (SD)			
Race, fraction (%)			
White			
Black			
Asian			
Disease extent, fraction (%)			
Proctitis only			
More extensive than proctitis			
Last Mayo endoscopic subscore, fraction (%)			
Normal or mild (≤1)			
Moderate (2)			
Severe (3)			
Extraintestinal manifestation, fraction (%)			
1 prior anti-TNF, fraction (%)			
>1 prior anti-TNF, fraction (%)			
Number of prior biologic or small molecule exposures, median (IQR)			
Prior immunomodulator, fraction (%)			
Current immunomodulator, fraction (%)			
Current corticosteroids, fraction (%)			
Current smoking, fraction (%)			
Current cannabis, fraction (%)			
Current opioids, fraction (%)			
SCCAI, mean (SD)			
Laboratory values			
Serum Albumin, mean (SD), g/dL			
CRP, mean (SD), mg/L			
Fecal calprotectin, median (IQR), µg/g			

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Table 3. Clinical Outcomes: Tofacitinib versus Ustekinumab

Outcomes	Tofacitinib	Ustekinumab	P-value
Steroid-free clinical remission, fraction 8-12 weeks (%)			
Steroid-free clinical remission, fraction 12 months (%)			
Endoscopic response, fraction (%)			
Endoscopic remission, fraction (%)			
Biochemical response, fraction (%)			
Improvement in extraintestinal manifestation, fraction (%)			
Colectomy, fraction (%)			
Complication, fraction (%)			

Table 4. Clinical Outcomes: Tofacitinib versus Vedolizumab

Outcomes	Tofacitinib	Vedolizumab	P-value
Steroid-free clinical remission, fraction 8-12 weeks (%)			
Steroid-free clinical remission, fraction 12 months (%)			
Endoscopic response, fraction (%)			
Endoscopic remission, fraction (%)			
Biochemical response, fraction (%)			
Improvement in extraintestinal manifestation, fraction (%)			
Colectomy, fraction (%)			
Complication, fraction (%)			

9.8. Quality Control

Data abstracted from electronic medical records will be reviewed by 2 study researchers to ensure accuracy. The statistical analysis will be conducted by 1 study researcher and then reviewed separately by a second study researcher.

9.9. Limitations of the Research Methods

Limitations include the retrospective study design and chart abstracted data which may be subject to omissions and documentation errors. Additionally, as the study takes place at a referral center, patients may have local care and gastroenterology data that may not be captured in medical records from MGB. However, whenever available, outside hospital records will be manually reviewed and data included as part of the data abstraction. This referral population, which typically has greater disease complexity, may also reduce the generalizability of results. There is also potential for confounding as there may be baseline differences in UC severity and acuity that may encourage providers to prescribe 1 treatment over another due to differences in onset of action between tofacitinib, ustekinumab, and vedolizumab. We will attempt to control for all relevant confounders possible using

propensity score weighting. However, there will be a possibility for residual, unmeasured confounding.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

As the study is entirely observational, there are no potential direct harms to patients. Patient anonymity and privacy will be protected by coding of all medical record numbers and removal of birth dates once data collection is completed. Codes for medical record numbers will be stored in a separate file which will be password protected and stored on a MGB computer and MGB Dropbox, accessible only by the researchers. The dataset to be analyzed will be de-identified.

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.

Patient personal data will be stored in a MGB computer and MGB Dropbox in encrypted electronic form, both of which are password protected to ensure that only authorized study staff have access. The MGB 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, MGB shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

This study has been approved as part of a larger protocol by the IRB of Brigham and Women's Hospital.

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) and the ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Human Review of Unstructured Data

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 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 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 AE report 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 1 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:

- Your Reporting Responsibilities (YRR) Training for Vendors.

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.

11.2. Structured Data Analysis

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an (AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Research abstracts will be submitted to American College of Gastroenterology Annual Meeting 2022 Advances in Inflammatory Bowel Diseases (AIBD) 2022, and/or Digestive Disease Week (DDW) 2023.

Manuscript draft will be submitted to Target journals include *Inflammatory Bowel Diseases*, *Clinical Gastroenterology and Hepatology*, *Journal of Crohn's and Colitis*, and *Alimentary Pharmacology and Therapeutics.*

A final study report will be written within 11 months after end of data collection.

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 MGB is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis. *Clin Gastroenterol Hepatol*. Sep 2020;18(10):2179-2191.e6. doi:10.1016/j.cgh.2020.01.008.

2. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. Nov 29 2021;doi:10.1016/S2468-1253(21)00377-0.

3. Dalal RS, Mitri J, Goodrick H, Allegretti JR. Real-World Comparison of Tofacitinib vs Ustekinumab Among Bio-Exposed Patients With Ulcerative Colitis: A Propensity Score Analysis. *Inflamm Bowel Dis*. May 14 2021;doi:10.1093/ibd/izab097.

14. LIST OF TABLES

LIST OF FIGURES

Redacted

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	08 April 2022	Comparative Effectiveness of Tofacitinib vs Ustekinumab and Vedolizumab among UC Patients with Prior Anti-TNF Failure

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.