NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Comparative Effectiveness of Tofacitinib Versus Vedolizumab among Ulcerative Colitis Patients With Prior Anti- Tumor Necrosis Factor (TNF) Failure
Protocol number	A3921415
Protocol version identifier	1.0
Date	08 February 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 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 after tofacitinib 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
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
Redacted	Redacted
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. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Redacted	Redacted	Pfizer Inc.	235 E. 42nd St. New York, 10017
Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Division of Redacted	Redacted

4. ABSTRACT

Stand-alone document. Please see ANNEX 1.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 March 2022
End of data collection	30 April 2022
Registration in the European Union (EU) PAS register	28 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 vedolizumab and tofacitinib 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 vedolizumab were not made. As tofacitinib and vedolizumab therapy are both commonly considered after failure of the anti-TNF class for UC, comparative data that reflect real-world outcomes are needed.

Recently conducted a real-world comparative effectiveness analysis of tofacitinib versus ustekinumab in bio-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 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 of 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 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]) at 8-12 weeks after tofacitinib or vedolizumab initiation among patients with prior anti-TNF exposure.
2. Compare proportions of corticosteroid-free clinical response (reduction in baseline SCCAI $\geq$2 if not available Mayo score by $\geq$2 points if not available by PGA) at 8-12 weeks.
3. Compare biologic survival (time to treatment discontinuation or colectomy) of tofacitinib versus 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-biologic 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 Weeks 8, 26, 52, and 96, where data is available.
3. Compare proportions of colectomy, inflammatory bowel disease (IBD)-related hospitalization, and corticosteroid use within 52 weeks of biologic initiation.
4. Compare proportions of patient-reported improvement in articular extraintestinal manifestations at 52 weeks after biologic initiation.
5. Compare proportions of potential complications (eg, infection, thromboembolism, shingles, new malignancy) during available follow-up.
6. Describe reasons for treatment discontinuation.

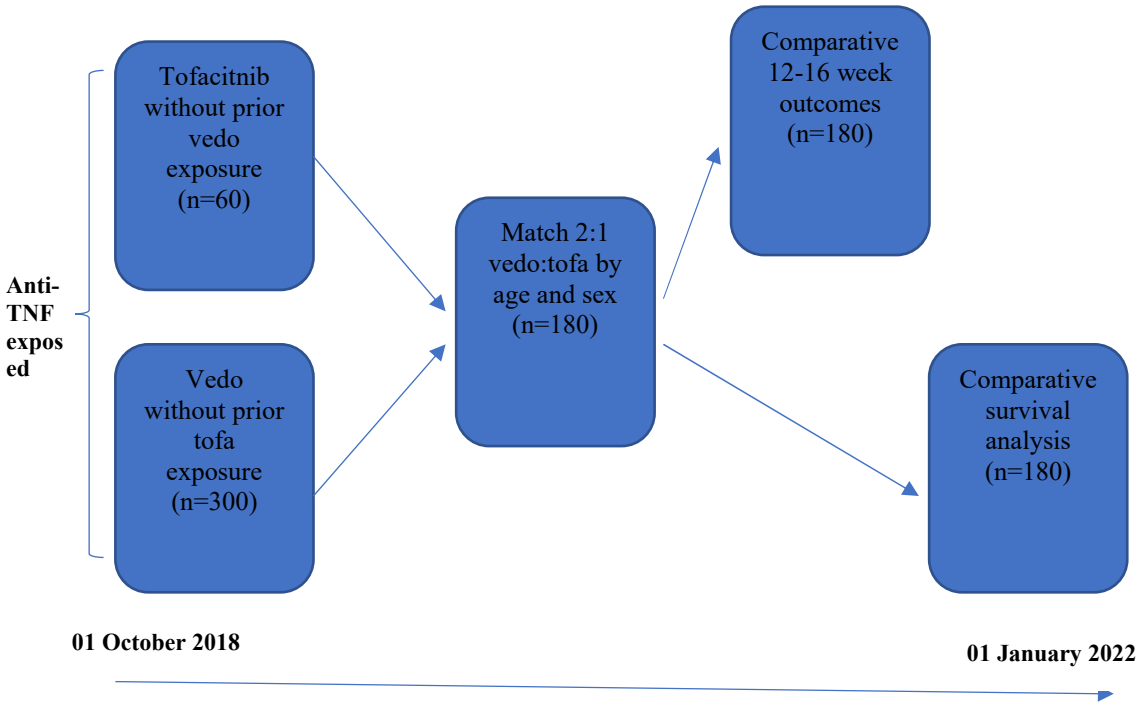
9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study of patients aged ≥18 years with UC who initiate tofacitinib or vedolizumab therapy on or after 01 October 2018 (month of tofacitinib US Food and Drug Administration [FDA] approval for UC) through 01 February 2022 in the [redacted]) health system. Patient cohorts for research are identified using the [redacted] Research Patient Data Registry (RPDR), which filters Epic (the electronic health record of [redacted]) 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. Patients previously exposed to other biologic classes will be excluded. Two vedolizumab patients will be matched for every 1 tofacitinib patient by age and sex using data automatically extracted from the RPDR. 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 after biologic initiation. Drug survival will also be assessed by following patients from the time of biologic 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 February 2022 (Figure 1). Independent variables to be abstracted are baseline characteristics present at the time of tofacitinib or vedolizumab initiation (or most recent available values within 3 months of initiation).

Figure 1. Study Design



9.2. Setting

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

3. Prior anti-TNF exposure.

4. Patient within the Redacted 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 or vedolizumab therapy is not ulcerative colitis.

3. Prior exposure to biologics other than anti-TNF agents.

4. Diagnosis of Crohn's disease or indeterminate colitis.

5. Dual biologic therapy (eg, tofacitinib and vedolizumab simultaneously).

9.3. Variables

Independent variables to be abstracted are baseline characteristics present at the time of tofacitinib 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	Redacted	Demographics
Sex	Baseline characteristic	Redacted	Demographics
Race/ethnicity	Baseline characteristic	Redacted	Demographics
Body mass index (BMI)	Baseline characteristic	Redacted	Demographics
UC duration (years)	Baseline characteristic	Redacted	Disease characteristics
Montreal disease extent	Baseline characteristic	Redacted	Disease characteristics
Mayo endoscopic severity score and histologic activity (based on last colonoscopy)	Baseline characteristic/Outcome	Redacted	Secondary endpoint
Mayo or SCCAI as documented in clinic notes	Baseline characteristic/Outcome	Redacted	Primary endpoint
Physician global assessment (PGA)	Baseline characteristic/Outcome	Redacted	Primary endpoint

Variable	Role	Data source(s)	Operational definition
Daily bowel movement frequency	Baseline characteristic/Outcome	Redacted	Disease characteristics
C-reactive protein	Baseline characteristic/Outcome	Redacted	Secondary endpoint
Serum albumin	Baseline characteristic	Redacted	Confounder
Fecal calprotectin	Baseline characteristic/Outcome	Redacted	Secondary endpoint
Concomitant and prior UC medications (corticosteroids, 5-ASA, azathioprine, 6-mercaptopurine, methotrexate, biologic therapies)	Exposure	Redacted	Prior Concomitant medication
Substance use (current cannabis, current opioids)	Exposure, Baseline characteristics	Redacted	Demographics
Smoking (current, former, or never)	Exposure, Baseline characteristics	Redacted	Demographics
History of malignancy	Baseline characteristics	Redacted	Disease characteristics
UC-related hospitalization within the last 12 months	Baseline characteristics	Redacted	Disease characteristics
History of Colectomy (if applicable)	Baseline characteristics	Redacted	Disease characteristics
Extraintestinal manifestation (presence at drug initiation and improvement after drug initiation)	Baseline characteristics/Outcome	Redacted	Disease characteristics/secondary endpoint
Adverse events (AE)	Outcome	Redacted	Safety Data/secondary endpoint
Tofacitinib intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Redacted	NA
Vedolizumab intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Redacted	NA
Reason for treatment discontinuation (primary/secondary loss of response, adverse event, colectomy for dysplasia)	Outcome	Redacted	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 Redacted using the pre-specified inclusion/exclusion criteria.

9.5. Study Size

The sample size that meets the inclusion/exclusion criteria is expected to be 60 patients in the tofacitinib group and 300 patients in the vedolizumab group per estimates from the RPDR. Two vedolizumab patients will be matched for every 1 tofacitinib patient by age and sex, resulting in a final sample of approximately 180 patients.

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 Redacted computer and Redacted 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. Redacted shall ensure that the DCTs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Redacted 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, Redacted 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 Redacted according to local regulations or as specified in the research agreement, whichever is longer. Redacted must ensure that the records continue to be stored securely for so long as they are retained.

If Redacted 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.

Redacted 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 Redacted using the pre-specified inclusion and exclusion criteria, vedolizumab patients will be matched 2:1 to tofacitinib patients by age (±3 years) and sex. The matched sample will be used for all subsequent analyses. 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 60 patients in the tofacitinib group and 300 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 matched for every 1 tofacitinib patient by age and sex, resulting in a final sample of approximately 180 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 0.87 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 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.

A multivariable logistic regression model will be built to determine the association of tofacitinib versus vedolizumab therapy with corticosteroid-free remission at 8-12 weeks and corticosteroid-free response at 8-12 weeks (2 separate models). Confounders for the model will be chosen *a priori* and will include BMI, Mayo endoscopic subscore, serum albumin, disease duration, current corticosteroid use, current immunomodulator use, and UC hospitalization within the prior 12 months.

A multivariable Cox proportional hazards modeling will be built to determine the association of tofacitinib versus vedolizumab therapy with drug survival (ie, time to biologic discontinuation or colectomy). The same confounders from the multivariable logistic regression models will be used. Kaplan-Meier analysis with log-rank test stratified by biologic will also be performed.

If the number of covariates exceeds the number of outcome events / 7, then propensity scores will be utilized to avoid model overfitting.[4] Propensity scores will be calculated using a logistic regression model to predict treatment of tofacitinib versus vedolizumab using baseline independent variables as covariates. The propensity scores will then be used to calculate inverse probability of treatment weights. This weighted sample will then be utilized for logistic and Cox regression analyses. Patients with missing data for any independent variables will be excluded from multivariable 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 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			
Left-sided			
Pancolitis			
Last Mayo endoscopic subscore, fraction (%)			
Normal or mild (≤1)			
Moderate (2)			
Severe (3)			
Extraintestinal manifestation, fraction			

Characteristics	Tofacitinib	Vedolizumab	P-value
(%)			
1 prior anti-TNF, fraction (%)			
>1 prior anti-TNF, fraction (%)			
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			
C-reactive protein, mean (SD), mg/L			
Fecal calprotectin, median (IQR), µg/g			

Table 2. Clinical Outcomes: Tofacitinib versus Vedolizumab

Outcomes	Tofacitinib	Vedolizumab	P-value
Steroid-free clinical remission, fraction (%)			
Steroid-free clinical response, fraction (%)			
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 [redacted]. 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 and vedolizumab. We will attempt to control for all relevant confounders possible using multivariable logistic and Cox regression and/or 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 Redacted computer and Redacted 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 Redacted computer and Redacted Dropbox in encrypted electronic form, both of which are password protected to ensure that only authorized study staff have access. Redacted 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, Redacted 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 Redacted and Redacted 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).

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 adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

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

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the adverse event 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 adverse event (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 AIBD 2022, and/or 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 Redacted 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.

4. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of Logistic Regression versus Propensity Score When the Number of Events Is Low and There Are Multiple Confounders. *American Journal of Epidemiology*. 2003;158(3):280-287. doi:10.1093/aje/kwg115.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	08 February 2022	Comparative Effectiveness of Tofacitinib vs Vedolizumab among Ulcerative Colitis Patients with Prior Anti-TNF Failure

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921415 Non Interventional Study Protocol Final 08Feb2022
Document Title:	A3921415 Non Interventional Study Protocol Final 08Feb2022

Signed By:	Date(GMT)	Signing Capacity
Redacted	10-Feb-2022 12:06:07	Redacted
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Redacted	11-Feb-2022 17:39:26	Redacted