NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	12- and 18-Month Outcomes and Long-Term Survival of Tofacitinib in Ulcerative Colitis
Protocol number	A3921416
Protocol version identifier	Version 1.0
Date	08 February 2022
EU Post Authorization Study (PAS) register number	EUPAS44985
Active substance	Tofacitinib citrate
Research question and objectives	This retrospective cohort study will assess real-world clinical outcomes at 12 and 18 months after initiation of tofacitinib therapy for ulcerative colitis. Assess proportions of clinical remission and corticosteroid-free clinical remission at Week 52 and 78 after tofacitinib induction in a real-world cohort of patients with ulcerative colitis (UC).
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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
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
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard deviation

Abbreviation	Definition
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			

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

Tofacitinib is an oral Janus kinase inhibitor that was approved for the treatment of moderate-to-severe UC in 2018. The Phase 3 OCTAVE clinical trials demonstrated the efficacy of induction and maintenance tofacitinib compared to placebo in this population.[1] A recent long-term extension study of OCTAVE open demonstrated that nearly 60% of patients who were in remission at baseline and 34% of all other patients maintained or achieve remission after 36 months of tofacitinib therapy.[2] However, data related to clinical trials may be less reflective of real-world clinical practice due to the strict exclusion criteria in such studies. Real-world outcomes of tofacitinib therapy in UC are currently limited.[3-7] A recent prospective Dutch cohort of 123 UC patients with prior failure of anti-tumor necrosis factor (TNF) and vedolizumab therapies identified a clinical remission rate of 27% at a median of 24 weeks after initiation of tofacitinib therapy and a 6% rate of adverse events (AEs) requiring therapy discontinuation.[6] Real-world outcomes of tofacitinib therapy at 52 weeks and beyond are nevertheless lacking. Therefore, the aim is to perform a retrospective cohort study to assess long-term clinical outcomes at 52 and 78 weeks of tofacitinib therapy for UC.

This non-interventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

This retrospective cohort study will assess real-world clinical outcomes at 12 and 18 months after initiation of tofacitinib therapy for ulcerative colitis.

Primary objective:

1. Assess proportions of clinical remission (Simple Clinical Colitis Activity Index [SCCAI] or Mayo ≤2 or physician global assessment [PGA]) and corticosteroid-free clinical remission (with no use of corticosteroids within 30 days preceding assessment) at Week 52 and 78 after tofacitinib induction in a real-world cohort of patients with UC.

Secondary objectives:

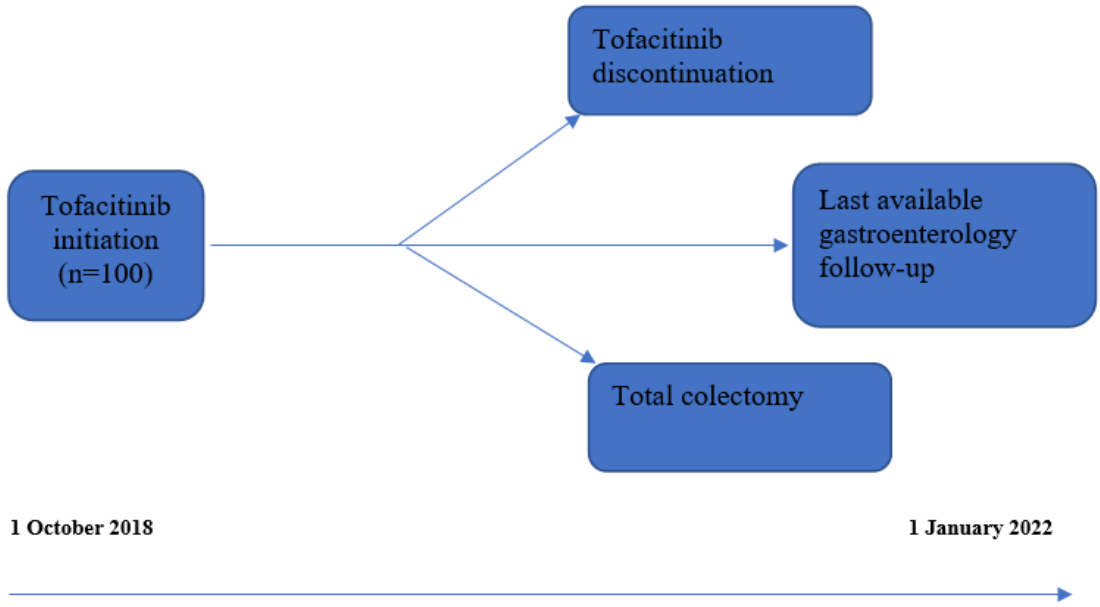
1. Use univariable and multivariable logistic regression to identify baseline predictors of corticosteroid-free clinical remission (with no use of corticosteroids within 30 days preceding assessment) at Weeks 52 and 78.
2. Use multivariable cox regression to identify baseline predictors of drug survival (ie, time to tofacitinib discontinuation or colectomy due to refractory disease activity).
3. Assess proportions of endoscopic response (ie, decrease in Mayo endoscopic subscore by 1 point) and endoscopic remission (Mayo endoscopic subscore <1) >8 weeks post-tofacitinib induction.
4. 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 78.
5. Describe proportions of dose de-escalation (10 to 5 mg) or dose re-escalation (5 to 10 mg) at any point during follow-up. Median times to dose changes will be reported.
6. Assess proportions of clinical remission and corticosteroid-free remission 8-16 weeks after does de-escalation and dose re-escalation.
7. Describe proportions of colectomy, inflammatory bowel disease (IBD)-related hospitalization (ie, UC listed as primary or secondary discharge diagnosis), and corticosteroid use within 52 weeks of tofacitinib induction.
8. Assess proportions of patient-reported improvement in articular extraintestinal manifestations at 52 weeks after tofacitinib induction (among those with articular manifestations at baseline).
9. Assess proportions of all possible complications (eg, infection, thromboembolism, shingles, new malignancy) that are documented during available follow-up.
10. 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 therapy after 01 October 2018 (month of Food and Drug Administration [FDA] approval) in the Redacted) health system. Patients will be followed from the time of tofacitinib initiation to tofacitinib discontinuation, total colectomy, or the last available gastroenterology encounter through 01 January 2022 (Figure 1). Independent variables will be recorded as the most recent values available within 3 months prior to tofacitinib initiation. Primary endpoint will be proportion of patients in clinical remission and corticosteroid-free clinical remission at Weeks 52 and 78, and secondary endpoints include clinical remission, drug survival (ie, treatment persistence), endoscopic response/remission, and biochemical response/remission.

Figure 1. Study Design



9.2. Setting

The study setting is the [Redacted], which includes [Redacted] in Massachusetts, United States of America (USA). Adult patients will be included if they initiated tofacitinib 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 initiation to tofacitinib discontinuation, total colectomy, or the last available gastroenterology encounter through 01 January 2022.

9.2.1. Inclusion Criteria

Participants 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 therapy for ulcerative colitis on or after 01 October 2018.

Patient within the MGB health system.

9.2.2. Exclusion Criteria

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

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

9.3. Variables

Independent variables to be abstracted are baseline characteristics present at the time of tofacitinib initiation (or most recent available values within 3 months of tofacitinib initiation). These will include but will not be 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
Daily bowel movement frequency	Baseline characteristic/Outcome	Redacted	Disease characteristics
C-reactive protein	Baseline characteristic/Outcome	Redacted ata	Secondary endpoint

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Variable	Role	Data source(s)	Operational definition
		Registry	
Serum albumin	Baseline characteristic/Outcome	Redacted	Confounder
Fecal calprotectin	Baseline characteristic/Outcome	Redacted	Secondary endpoint
Concomitant UC medications (corticosteroids [budesonide, prednisone, methylprednisolone], 5-ASA, azathioprine, 6-mercaptopurine, methotrexate, biologic therapies)	Exposure	Redacted	Concomitant medication
Prior UC medications (5-ASA, azathioprine, 6-mercaptopurine, methotrexate, biologic therapies)	Exposure	Redacted	Prior 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 y	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 y	Disease characteristics/secondary endpoint
Adverse events (AEs)	Outcome	Redacted	Safety Data/Secondary endpoint
Tofacitinib intake (initiation date, dose taken and any change of dosage, discontinuation)	Exposure/Outcome	Redacted	NA

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 estimated sample size is 100 patients per the Redacted Research Patient Data Registry. Among these, approximately 85 patients will have 12 or more months of follow-up. The primary objective is to describe the proportion of patients in clinical remission and corticosteroid-free clinical remission at 52 and 78 weeks, and for this p-values are not calculated. It is hypothesized, based on prior data, that approximately 40% or more of patients will be in corticosteroid-free clinical remission at these timepoints.

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.

The investigator 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 investigator 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, eg, CRFs/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

De-identified data will be imported into StataSE 17 for statistical analysis.

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.

The estimated sample size is 100 patients per the Redacted. Among these, approximately 85 patients will have 12 or more months of follow-up. The primary objective is to describe the proportion of patients in clinical remission and corticosteroid-free clinical remission at 52 and 78 weeks, and for this p-values are not calculated (similarly, a power calculation is not relevant for the primary outcomes). We hypothesize, based on prior data, that approximately 40% or more of patients will be in corticosteroid-free clinical remission at these timepoints.

Univariate and multivariable logistic regression models will be used to identify predictors (among all independent variables) of corticosteroid-free remission at Week 52 and week 78 (2 separate models). Variables from the univariable analysis that are statistically significant at $p<0.10$ will be included in the final multivariable model. Adjusted odds ratios with 95% confidence intervals will be calculated using logistic regression models and reported in the final models. Patients who die prior to assessment of endpoints will be excluded from the logistic regression analysis.

A Kaplan-Meier curve showing the survival function (ie, time to drug discontinuation) of tofacitinib therapy will be generated. Univariable and multivariable Cox proportional hazards modeling will be used to identify predictors (among all independent variables) of tofacitinib drug survival 8. Variables on univariable analysis associated with drug survival at $p<0.10$ will be included in the final multivariable model. Patients will be censored at time of colectomy, treatment discontinuation, death, or loss to follow-up. The proportional hazards assumption will be tested using Schoenfeld residuals. Adjusted hazard ratios with 95% confidence intervals will be reported in the final model. Patients with missing data for any independent variables will be excluded from multivariable analyses. StataSE 17 will be used for all analyses.

Sample result tables are included below.

Table 1. Baseline Characteristics

Characteristics	Tofacitinib
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 (%)	
>1 prior biologics, fraction (%)	
>2 prior biologics, fraction (%)	
Prior immunomodulator, fraction (%)	
Current immunomodulator, fraction (%)	
Current corticosteroids, fraction (%)	
Current smoker, fraction (%)	
Former but not current smoker, fraction (%)	
Never smoker, fraction (%)	
Current cannabis, fraction (%)	
Current opioids, fraction (%)	
SCCAI, mean (SD)	
Laboratory values	
Serum Albumin, mean (SD), g/dL	

Characteristics	Tofacitinib
C-reactive protein, mean (SD), mg/L	
Fecal calprotectin, median (IQR), µg/g	

Table 2. Clinical Outcomes

Outcomes	Tofacitinib
Clinical remission 52 weeks, fraction (%)	
Steroid-free clinical remission 52 weeks, fraction (%)	
Clinical remission 78 weeks, fraction (%)	
Steroid-free clinical remission 78 weeks, fraction (%)	
Endoscopic response, fraction (%)	
Endoscopic remission, fraction (%)	
Biochemical response, fraction (%)	
Improvement in articular extraintestinal manifestation, fraction (%)	
Colectomy, fraction (%)	
Complication, fraction (%)	

9.8. Quality Control

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

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. Patients who are lost to follow-up may not have subsequent outside records available, and this is also a limitation to the study.

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

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 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 one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will

be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

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

All research staff members must complete the following Pfizer training requirements:

- “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 AIBD 2022, and/or DDW 2023. Manuscript draft will be submitted to Target journals including *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 the 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. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med*. 05 2017;376(18):1723-1736. doi:10.1056/NEJMoa1606910.

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7. Jameshorani M, Vahedi H, Sadeghi A, et al. Efficacy and Safety of Tofacitinib for Treatment of Moderate to Severe Active Ulcerative Colitis: First Report from Iran. *Arch Iran Med*. 05 01 2021;24(5):354-363. doi:10.34172/aim.2021.52.

8. Myers J. Survival analysis techniques in clinical research. *J Ky Med Assoc*. Nov 2007;105(11):545-50.

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	12- and 18-Month Outcomes and Long-Term Survival of Tofacitinib in Ulcerative Colitis

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921416 Non Interventional Study Protocol Final 08Feb2022
Document Title:	A3921416 Non Interventional Study Protocol Final 08Feb2022

Signed By:	Date(GMT)	Signing Capacity
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