NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Real World Evidence of the Usage of tofacitinib in Ulcerative Colitis Patients in Lebanon
Protocol number	A3921393
Protocol version identifier	Version 1
Date	19 May 2021
EU Post Authorization Study (PAS) register number	EUPAS38515
Active substance	ATC: L04AA29
Medicinal product	Tofacitinib
Research question and objectives	To describe the effectiveness of tofacitinib in patients with ulcerative colitis in a Lebanese cohort Primary objectives: • To evaluate the real world (RW) effectiveness of tofacitinib in ulcerative colitis patients by improvement in the proportion of patients achieving clinical remission and proportion of patients achieving endoscopic remission and response. Secondary Objectives: • To further evaluate the RW effect of tofacitinib treatment including proportion of patients that are still on tofacitinib treatment, proportion of patients undergoing inflammatory

	bowel disease (IBD) surgery, and lab parameters changes from baseline.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEM	Adverse Event Monitoring
AEs	Adverse events
AUBMC	American University of Beirut Medical Center
CD	Crohn's Disease
COOP	Cooperative of government employees
CRF	Case report form
CRP	C-reactive protein
EU	European Union
FDA	Federal Drug Administration
HZV	Herpes zoster virus
IBD	Inflammatory bowel disease
ICMJE	International committee of medical journal editors
JAK	Janus Kinase
LDL	Low-density lipoprotein
NI	Non-interventional
NIS	Non-interventional study
NSSF	National social security fund
PAS	Postauthorization safety
PASS	Postauthorization safety study
RCT	Randomized controlled trials
RW	Real world

Abbreviation	Definition
RWD	Real world data
SPSS	Statistical package for social sciences
TNF	Tumor necrosis factor
UC	Ulcerative colitis
YRR	Your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Ala Sharara, MD, FACG, AGAF, FRCP	Professor of Medicine	AUBMC	P.O. Box 11-0236, Riad El-Solhm, Beirut, Lebanon
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4. ABSTRACT

In Annex 1 as a stand-alone document.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Registration in the European (EU) PAS register	17 May 2021
Start of data collection	31 August 2021
End of data collection	31 December 2021
Final study report	30 November 2022

7. RATIONALE AND BACKGROUND

Ulcerative Colitis is a chronic inflammatory bowel disease with a relapsing-remitting pattern that causes an increased frequency of bowel movements and bloody diarrhea, leading to organ damage and impaired quality of life.[1] The primary goals of therapy in ulcerative colitis (UC) are reducing the mucosal inflammation and maintaining symptom remission, though these aims are not achieved in all patients.[1] Despite the array of medical options available, treatment failure is common and refractory disease represents an unmet clinical need.[2] Hence, additional treatments including those with different new modes/mechanisms of actions are needed.

Tofacitinib, an inhibitor of the Janus Kinase (JAK) family of kinases, was approved in Lebanon in August 2018 at a dose of 5 mg or 10 mg twice daily for the treatment of adults with moderate-to-severe UC, who have had an inadequate response or who are intolerant to tumor necrosis factor (TNF) blockers. The efficacy profile and safety profile of tofacitinib have been demonstrated as induction and maintenance therapy in 3 Phase 3, randomized, placebo-controlled trials in patients with moderate to severe ulcerative colitis.[2] However, the study design and procedures in the previous randomized controlled trials (RCT) may not always reflect the clinical practice. It is important to clinicians, patients, and payers to ascertain the outcomes in the Lebanese environment where the drug is used.

Real world data has become increasingly important in providing additional evidence of treatment effectiveness in clinical practice. Real world data (RWD) on the use of tofacitinib in ulcerative colitis had not been reported previously in Lebanon, where is the need to conduct this study. The use of observational clinical data collected from the patients during regular treatment visits will allow for the generation of data on the induction, maintenance, and long term effectiveness of tofacitinib in Lebanon outside the confines of the RCT.

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

The objective of this study is to describe the effectiveness of tofacitinib in the treatment of ulcerative colitis in a Lebanese cohort:

Primary objectives:

- To evaluate the real world (RW) effectiveness of tofacitinib in ulcerative colitis patients by improvement the proportion of patients achieving clinical remission and proportion of patients achieving endoscopic remission and response.

Secondary Objectives:

- To further evaluate the RW effect of tofacitinib treatment including proportion of patients that are still on tofacitinib treatment, proportion of patients undergoing IBD surgery, and lab parameters changes from baseline.

9. RESEARCH METHODS

9.1. Study Design

This is an observational retrospective cohort study that describes the effectiveness of tofacitinib for the treatment of patients with ulcerative colitis in Lebanon. Data of patients meeting the inclusion criteria will be extracted from the database of the American University of Beirut Medical Center (AUBMC). It is estimated that data of about 120 patients who have received treatment with tofacitinib for UC in Lebanon, with minimal follow-up period of 12 weeks will be included.

Primary endpoints:

- Proportion of patients achieving clinical remission*by 8 weeks, 26 weeks, and 52 weeks.
- Proportion of patients achieving endoscopic remission* and response* in ulcerative colitis as determined by the endoscopic Mayo score at 24 weeks.

Secondary Endpoints:

- Proportion of patients that are still on tofacitinib treatment at 1 year.
- Proportion of patients requiring IBD surgery after 1 year of follow up.
- Changes in calprotectin at 12 weeks compared to baseline following treatment with tofacitinib.
- Changes in C-reactive protein (CRP) at 12 weeks compared to baseline following treatment with tofacitinib.
- Changes in hemoglobin at 12 weeks compared to baseline following treatment with tofacitinib.
- Changes in Low-density lipoprotein (LDL) at 12 weeks compared to baseline following treatment with tofacitinib.

**Clinical remission is defined as per reported by the treating physician, Endoscopic remission is defined as endoscopic Mayo score of 1 or 0, endoscopic response is defined as at least 1 grade improvement from baseline of endoscopic Mayo score.*

9.2. Setting

This study is a retrospective cohort study collecting data from patients with ulcerative colitis. The data will be extracted from the database of the AUBMC, a university hospital in Beirut. The data collection will occur over a period of 4 months. The patients included are UC patients who started treatment on tofacitinib and fulfill the below inclusion and exclusion criteria.

9.2.1. Inclusion Criteria

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

1. Male or female patients 18 years or older by the time of starting tofacitinib treatment
2. Confirmed diagnosis of ulcerative colitis.
3. Patients who have received treatment with tofacitinib for ulcerative Colitis with minimal follow-up period of 12 weeks.

9.2.2. Exclusion Criteria

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

1. Current or previous (within the last 2 years) indeterminate or not classified colitis.
2. Changing of IBD type (ie, from UC to Crohn's disease (CD), etc.) within the last 2 years.
3. Any combinations of tofacitinib with other advanced therapies.
4. Any previous use and discontinuation of tofacitinib.

9.3. Variables

Table 1. Endpoints Time Windows

Endpoint	Time window
Clinical remission at 8 weeks	8 weeks ±4 weeks
Clinical remission at 26 weeks	26 weeks ±4 weeks
Clinical remission at 52 weeks	52 weeks ±6 weeks
Endoscopic remission at 24 weeks	24 weeks ±4 weeks
Endoscopic response at 24 weeks	24 weeks ±4 weeks

Endpoint	Time window
Patients that are still on tofacitinib treatment at 1 year	52 weeks ±6 weeks
Patients requiring IBD surgery after 1 year of follow up	52 weeks ±6 weeks
Changes in CRP, calprotectin, hemoglobin and LDL at 12 weeks compared to baseline following treatment with tofacitinib	12 weeks +8 weeks

Variable	Role	Data source(s)	Operational definition
Patient demographics and medical history			
Age	Baseline characteristics	AUBMC database	Demographics, medical history, and concomitant/prior medication of patients.
Gender			
Smoking status			
Herpes zoster virus (HZV) testing prior to tofacitinib initiation			
Concomitant medication			
Prior medication			
Co-morbidities			
Disease characteristics			
Age at diagnosis	Baseline characteristics	AUBMC database	Patient age in years at time of UC diagnosis.
Disease extent			Ulcerative proctitis; left sided UC; extensive UC
Extra intestinal manifestations of the disease			peripheral arthropathy; axial involvement; sweet syndrome; uveitis; erythema nodosum; episcleritis; scleritis; pyoderma gangrenosum; oral aphthous ulcers; primary sclerosing cholangitis; none
Tofacitinib treatment			
Method of dispensation of tofacitinib	Baseline characteristic	AUBMC database	Ministry of health; National social security fund (NSSF); Cooperative of government employees (COOP); armed forces;

Variable	Role	Data source(s)	Operational definition
			self-payer
Tofacitinib intake	Exposure	AUBMC database	Dose; duration of treatment up to the point of data extraction; tofacitinib dosage adjustment following induction
Medical assessments			
Endoscopy	Primary endpoint component	AUBMC database	Mayo score at initiation of tofacitinib therapy (0-12)
Laboratory	Secondary endpoints	AUBMC database	CRP (mg/L), calprotectin (µg/mg), hemoglobin (g/dl), LDL cholesterol (mg/dl)
Safety			
Adverse events (AE)	Exposure	AUBMC database	Type of adverse events

9.4. Data Sources

Data will be extracted from the database at the AUBMC and entered into electronic case report form (CRF). The data does not contain personalized information. Data will be collected on patient's demography, disease features, treatment history, lab parameters, clinical and endoscopic assessments before and after tofacitinib treatment, tofacitinib treatment withdrawal and adverse events.

9.5. Study Size

Based on the feasibility assessment, the number of patients on tofacitinib for ulcerative colitis in Lebanon is estimated to be 120. The study aims to capture almost the entire population.

9.6. Data Management

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

As used in this protocol, the term CRF 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 CRF is required and should be completed for each included patient. The completed original CRFs 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. The AUBMC, acting also as the contract research organization (CRO) in this study, shall ensure that the CRFs are securely stored at AUBMC research location in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

AUBMC has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs 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 CRFs must be signed by AUBMC or by an authorized staff member of AUBMC to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs 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 CRFs must match those charts.

9.6.2. Record Retention

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

If AUBMC 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, unless AUBMC and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

9.7. Data Analysis

All collected data will be analyzed. Analysis will be done by the Statistical Program for the Social Sciences (SPSS). All covariates will be summarized to get information about frequency distribution and mean, median or standard deviation. Numbers and percentages of patients who are in complete remission will be presented for weeks 8, 26, and 52 when performing descriptive analysis of categorical data. Means, medians, standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data.

The bivariate analysis will be conducted to determine if there is any association between the outcome and the exposure (the covariates). Unadjusted comparisons of baseline characteristics for 8, 26, and 52 weeks after complete remission against outcome measures will be provided. Appropriate tests will be used based on the distribution of the measure: proportions will be provided by Fisher's exact test, means will be provided by 1 sample t-test and medians provided by 1-sample Wilcoxon test; p-values will also be generated. Time to treatment failure will be described through Kaplan-Meier estimates , and median time to event will be presented with 25th and 75th percentiles of treatment failure will be calculated. The proportional hazard and odds ratio will be presented.

The safety of tofacitinib will be described by the number and types of adverse events suffered by the patients.

9.8. Quality Control

Data will be entered manually into the CRF by medically qualified personnel. Entered data will be reviewed and compared to source data by another personnel to avoid data entry errors.

9.9. Limitations of the Research Methods

- Missing or incomplete data could be a limitation of the study.
- This study does not have a comparator Arm as no data for contextualization is available.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

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.

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 American University of Beirut Medical Center (AUBMC) 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)

This study requires IRB approvals at AUBMC, there is no independent ethics committee, the ethical approval is within the IRB. There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRB.

All correspondence with the IRB will be retained. Copies of IRB approvals will 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 Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 CRF 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 Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

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.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS:

At the end of the study, a final report will be submitted within 11 months. Research results from this study will be published in peer reviewed scientific journal. The Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors (ICMJE)

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 AUBMC 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. Chaparro M et al, Tofacitinib in Ulcerative Colitis: Real-world Evidence From the ENEIDA Registry. J Crohns Colitis. 2021 Jan 13;15(1):35-42.

2. Deepak P et al, Safety of Tofacitinib in a Real-World Cohort of Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2020 Jul 3:S1542-3565(20)30913-7.

14. LIST OF TABLES:

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
Number 1	Not applicable	19 May 2021	Abstract: Real World Evidence of the Usage of Tofacitinib in Ulcerative Colitis Patients in Lebanon

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
Sunna, Nancy	01-Jul-2021 10:39:59	Manager Approval
Chambers, Richard Burtin	02-Jul-2021 14:05:20	Business Line Approver
De Bernardi, Barbara	05-Jul-2021 13:46:57	EUQPPV Approval