NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Retrospective non-interventional multicenter patient chart data study on tofacitinib real-world experience in ulcerative colitis in Finland (FinTofUC)
Protocol number	A3921390
Protocol version identifier	Version 1
Date	01 July 2021
Active substance	ATC L04AA29
Medicinal product	Tofacitinib (Xeljanz)
Research question and objectives	To identify key characteristics of patients treated with tofacitinib for ulcerative colitis and describe the real-world effectiveness of tofacitinib for the treatment of ulcerative colitis in Finland.
Author	PPD PPD , NI study lead, Pfizer Finland PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
AE	adverse event
ATC	anatomic therapeutic chemical classification system
B-hb	blood hemoglobin
B-leuk	blood leukocytes
B-ly	blood lymphocytes
B-neutr	blood neutrophiles
B-thromb	blood thrombocytes
BMI	body mass index
CRO	clinical research organization
eDMT	electronic data mining tool
EHR	electronic health record
EIM	extraintestinal manifestations
ERVA	erityisvastuualue
f-calpro	fecal calprotectin
FPFV	first patient first visit
GPP	good pharmacoepidemiology practices
HUS	Helsinki University Hospital
IBD	inflammatory bowel disease
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th revision

Abbreviation	Definition
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IPAA	ileal pouch-anal anastomosis
JAK	Janus kinase
LPLV	last patient last visit
NI	non-interventional
P-CRP	plasma C-reactive protein
P-alb	plasma albumin
pMayo	partial Mayo
QC	quality control
QoL	quality of life
RCT	randomized controlled trial
RWE	real-world evidence
SAP	statistical analysis plan
STAT	signal transducers and activators of transcription
TyK2	tyrosine kinase 2
UC	ulcerative colitis

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD	PPD	PPD	PPD
PPD, MD	PPD	PPD	PPD
PPD	PPD	PPD	PPD
PPD MD	PPD	PPD	PPD
PPD, MD	PPD	PPD	PPD
PPD	PPD	PPD	PPD
PPD, PhD	PPD	PPD	PPD
PPD, PhD	PPD	PPD	PPD

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	01 December 2021
End of data collection	30 May 2022
Final study report	01 May 2023

6. RATIONALE AND BACKGROUND

Inflammatory bowel diseases (IBD) is an umbrella term used to describe disorders that involve chronic inflammation of the digestive tract. IBD includes ulcerative colitis (UC) and Crohn's disease. More than 50,000 Finns suffer from IBD[1] with approximately 2,000 new cases diagnosed each year.[2] UC is a chronic, relapsing systemic disease that mainly affects the gastrointestinal tract, resulting in acute and chronic intestinal inflammation. It is characterized by inflammation in the large bowel (colon). Typical symptoms include blood in stool, diarrhea, urgency, and fatigue, and often the disease has substantial consequences for work participation and sick leave. The annual incidence of UC in Finland is about 25 new cases per 100,000 inhabitants. The prevalence is estimated at 550/100,000 inhabitants.[3] Based on data from the Social Insurance Institution of Finland, the incidence of UC in Finland between 2000–2007 is 2.5–3 times higher than that of Crohn's disease.[4] The steady increase in the incidence of UC in Finland from the beginning of the 21st century to 2007 was demonstrated in a registry study of Social Insurance Institution of Finland compensation conducted by Jussila et al.[5]

Tofacitinib is an oral Janus kinase (JAK) inhibitor indicated for the treatment of several immune-mediated diseases including UC. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (eg, JAK1/JAK3, JAK1/JAK2, JAK1/tyrosine kinase 2 (TyK2), JAK2/JAK2).[6] Tofacitinib inhibited the in vitro activities in particular of JAK1/JAK3.[7] However, the relevance of specific JAK combinations to therapeutic effectiveness is largely unknown. The efficacy and safety of tofacitinib has been demonstrated as induction and maintenance therapy in 3 Phase 3, randomized, placebo-controlled trials in patients with moderate to severe UC.[8-10] However, the study design and procedures in the randomized controlled trial (RCT) may not always reflect clinical practice and treatment patterns. Thus, it is of interest to clinicians, patients, and taxpayers to describe outcomes in the environment where the drug will be used.

Real world evidence (RWE) has become increasingly important in providing additional evidence of treatment effectiveness in clinical practice. RWE data for tofacitinib has been published for rheumatoid arthritis and an overview of these data has recently been provided[11] while currently the primary sources of data for tofacitinib in UC patients is from the clinical development program including induction, maintenance, and long term extension studies in controlled patient populations.[10]

The use of observational data will allow for the generation of data on the induction, maintenance, and effectiveness of tofacitinib outside the confines of the RCT. Examples of additional data that can be collected using the non-interventional, registry data collection includes fecal calprotectin levels - a predictor of clinical and endoscopic outcomes, extraintestinal manifestations - conditions often observed in patients with IBD and dose changes outside of the construct of the clinical trial setting.

The aim of UC treatment is to achieve remission, improve quality of life (QoL) and avoid complications from the disease including surgeries and hospital admissions as well as side-effects from long-term corticosteroid use. Despite existing treatment with mesalazine, immunomodulators and biologics, severe disease and complications are common in UC. Hence, additional treatments including those with different new modes/mechanisms of actions are needed.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe and evaluate real-world data of tofacitinib for the treatment of UC in Finland in terms of clinical outcomes, treatment lines, and to identify the key characteristics of the patients treated with tofacitinib.

7.1. Definitions

Active disease:

- An endoscopic Mayo sub-score[12] of ≥2 or fecal-calprotectin (f-calpro) >250mg/kg.

Clinical response:

- A full Mayo score[12] decrease of ≥3 points and a decrease of ≥30% from baseline, with a decrease of ≥1 point on the rectal bleeding sub score or an absolute rectal bleeding score of ≤1.
- A partial Mayo score (ie, Mayo score without endoscopic assessment) decrease of ≥2 points and reduction of at least 25% in partial Mayo (pMayo) score from baseline with an accompanying decrease in rectal bleeding sub score of ≥1 point or absolute rectal bleeding sub score of ≤1.

Clinical remission:

- A full Mayo score of ≤2 points with no individual sub score exceeding 1 point, with rectal bleeding sub-score of 0.
- A pMayo score <2 points with rectal bleeding sub-score of 0.

7.2. Primary Objective

7.2.1. To Characterize the UC Patient Group Treated with Tofacitinib.

a. Patient demographics at tofacitinib treatment initiation: age, gender, weight, height, smoking status, body mass index (BMI), treating hospital.

b. Disease characteristics: age at diagnosis, duration of disease, and extent of colonic involvement according to the Montreal classification: E1 (ulcerative proctitis), E2 (left sided, distal colitis), E3 (pancolitis).

c. Disease severity as assessed by Mayo score and f-calpro at the initiation of tofacitinib use.

d. Laboratory results for biochemical inflammatory markers plasma C-reactive protein (P-CRP), blood thrombocytes (B-thromb), plasma albumin (P-alb), blood leukocytes (B-leuk), blood lymphocytes (B-ly), blood neutrophiles (B-neutr), blood hemoglobin (B-hb) and f-calpro at the start of tofacitinib treatment (baseline data).

e. Endoscopic findings including histology at the start of tofacitinib treatment (baseline data).

7.3. Secondary objectives

7.3.1. To Assess the Real-world Effectiveness of Tofacitinib.

a. Proportion of patients who are taking tofacitinib at week 8, 16, 24 and 52.

b. To assess rates of clinical remission defined by a full or partial Mayo score at week 8, 16, 24 and 52.

c. To assess rates of clinical response defined by a full or partial Mayo score at week 8, 16, 24 and 52.

d. Proportion of patients in steroid-free clinical remission at weeks 8, 16, 24, and 52 as defined by full or partial Mayo who did not require any corticosteroid treatment during the period ≥4 weeks prior to the visit (for all patients and for those treated with corticosteroids at baseline).

e. Proportion of patients reaching clinical response as defined by full or partial Mayo score at week 8, 16, 24 and 52.

f. Time to response as assessed by a decrease as defined by full or partial Mayo score.

g. Proportion of responders defined by a f-calpro reduction of ≥50%, ≥75% or ≥90% at week 8, 16, 24 and 52 compared to baseline.

h. Proportion of patients reaching f-calpro below 250 mg/kg at week 8, 16, 24 and 52 of those that had f-calprotectin above 250 mg/kg at baseline and change from baseline in f-calpro at week 8, 16, 24 and 52.

i. Proportion of patients in sustained remission (pMayo and full Mayo score) from week 8 to week 16, 24 and 52.

j. Proportion of patients in sustained remission (pMayo and full Mayo score) from week 16 to week 24 and 52.

k. Proportion of patients in sustained steroid free remission (pMayo and full Mayo score) at week 16 to 24 and 52 (for all patients and for those treated with corticosteroids at baseline).

l. Change in partial and full Mayo score at weeks 8/16/24/52.

m. Proportion of patients in sustained endoscopic remission (sub score = 0), mucosal healing (sub score 0-1) or endoscopic response (sub score reduction from baseline of ≥1) from week 8 to week 16, 24 and 52.

n. Proportion of patients in physician assessed histological remission determined as inactive disease, or normal histology, and change from baseline in histology assessment (0= normal histology, 1= inactive disease and 2 = active disease) at week 8/16/24/52.

o. Proportion of patients in sustained steroid free remission (pMayo and full Mayo score) (for all patients and for those treated with corticosteroids at baseline) and endoscopic remission (sub score = 0), mucosal healing (sub score 0-1) or endoscopic response (sub score reduction from baseline of ≥1) from week 8 to week 16, 24 and 52.

p. Comparison of response and remission (pMayo and full Mayo score) based on the extent of colonic involvement.

q. Proportion of patients with corticosteroid tapering at weeks 8/16/24/52 and their tapering rates and doses.

r. Proportion of patients with improvement in stool frequency sub score of 1 or more points and change from baseline in stool frequency sub score at week 8, 16, 24 and 52.

s. Proportion of patients with improvement in rectal bleeding sub score of 1 or more points and change from baseline in rectal bleeding sub score at week 8, 16, 24 and 52.

t. Proportion of patients reaching normal P-CRP levels (below 4mg/L) and change from baseline in P-CRP levels at week 8/16/24/52.

u. Proportion of patients reaching normal B-hb levels (men: 134–167 g/L, women: 117–155 g/L) and change from baseline in B-hb levels at week 8/16/24/52.

v. Proportion of patients reaching normal B-leuk levels (3.4-8.2 x 10^9/L) and change from baseline in B-leuk levels at week 8/16/24/52.

w. Proportion of patients reaching normal B-Thromb (150–360 x 10^9/L) and change from baseline in B-Thromb levels at week 8/16/24/52.

x. Proportion of patients reaching normal B-ly (1.3-3.6 x 10^9/L) and change from baseline in B-ly levels at week 8/16/24/52.

y. Proportion of patients reaching normal B-neutr (1.5-6.7 x 10^9/L) and change from baseline in B-neutr levels at week 8/16/24/52.

z. Proportion of patients reaching normal P-alb (18-39 years: 36-48 g/L, 40-69 years: 36-45 g/L, 70 years and over: 34-45 g/L) and change from baseline in P-alb levels at week 8/16/24/52.

aa. Proportion of patients with extended tofacitinib induction dose (additional 8 weeks with 10mg).

bb. Real-world dosing of tofacitinib, eg, usage of a higher dose (10 mg) as maintenance therapy.

cc. Survival without drug discontinuation, colectomy or UC-related hospitalization (using time to event analysis).

7.3.2. To Assess Treatment Lines Prior to Tofacitinib Treatment.

a. Number and type of previous UC treatments.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

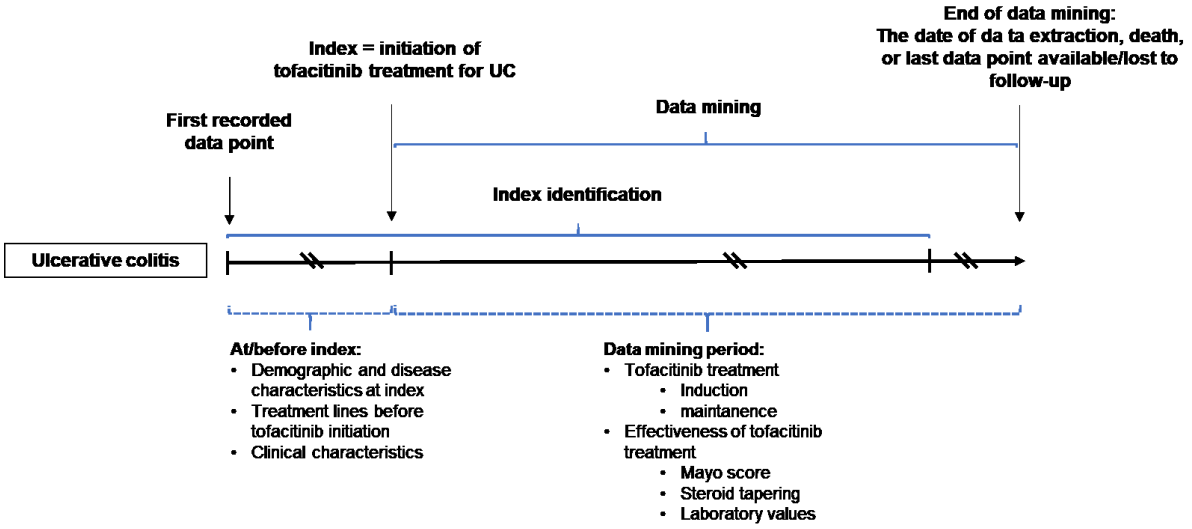
8. RESEARCH METHODS

8.1. Study Design

This is a retrospective non-interventional multicenter patient chart data study collecting real world data of tofacitinib treated patients with UC from 21 Finnish hospital district and Helsinki city hospital (included in "hospital districts" hence forward for the purpose of this protocol) databases and for whom data is available. Real-world data through health care registers is an excellent means to understand the tofacitinib treatment and use landscape in Finland.

The main purpose is to characterize the patient population receiving tofacitinib, their demographics and clinical characteristics. Patient characteristics before and after the use of tofacitinib will be determined for all patients. If possible, depending on patient numbers from different areas, regional differences will also be analyzed.

Figure 1. Schematic View of Study Flow



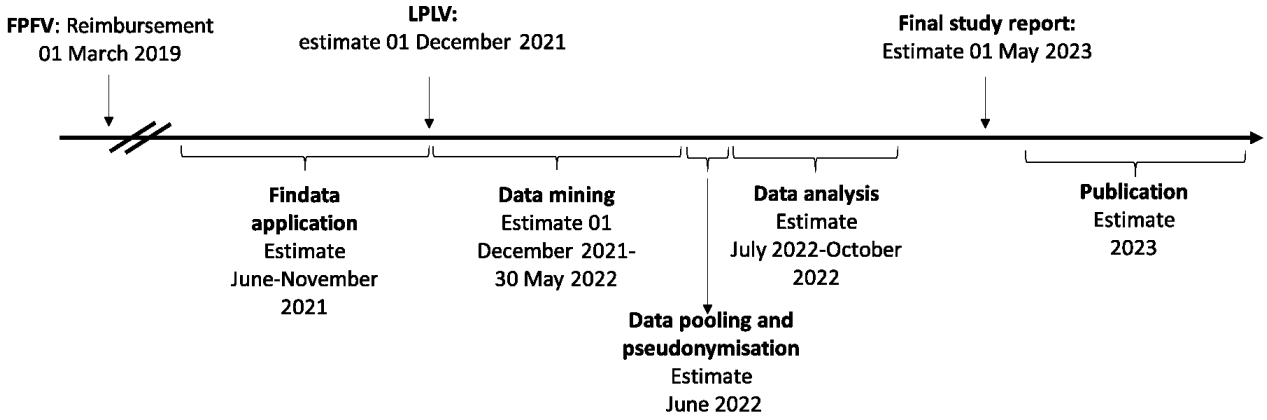
8.2. Setting

The target population for this study is adult ulcerative colitis patients who were prescribed tofacitinib. Estimated number of patients in this study is 100-150, with the aim of covering all ulcerative colitis patients in Finland treated with tofacitinib. The main inclusion criteria are a diagnosis of ulcerative colitis (ICD-10: K51) between January 2010 and December 2021 and treatment with tofacitinib. The main exclusion criteria are age under 18 years, use of tofacitinib before national reimbursement decision on 01 March 2019 and history of panproctocolectomy, ileal pouch-anal anastomosis (IPAA) or ileostomy.

The data collected has been generated as part of standard clinical care, treatment, and follow-up of ulcerative colitis patients. In accordance with the Finnish Act on Secondary Use of Health and Social Data 552/2019 (in Finnish: Laki sosiaali- ja terveystietojen toissijaisesta käytöstä), health registry data can be processed in scientific studies without patient consent. The purpose of this act is to establish conditions for the effective and secure processing of, and access to, personal health and social data for certain secondary purposes, such as research and statistics, innovation and development, knowledge management, teaching and authority planning. Thus, the Secondary Act creates a clear legal basis for the use of such registered data for research and innovation related to, for example, the health and well-being of citizens, the prevention of disease and the development of new treatment methods. This relatively new legislation is also a welcome unification of the fragmented Finnish national rules regarding the use of healthcare and social welfare data. In addition, it takes into consideration current data protection requirements.

The data will be collected by data miners in all hospital districts across Finland and entered into an electronic data mining tool (eDMT) which will be designed for the study in collaboration with Finnish clinicians. The data will be used to investigate and describe the patient population, treatment strategies and disease development.

Figure 2. Study Timeline



FPFV= First patient first visit, LPLV= Last patient last visit.

Please note that dates are subject to change depending on how long permit process with Findata takes.

8.2.1. Inclusion Criteria

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

1. Xeljanz (tofacitinib) usage for ulcerative colitis.
2. Diagnosis of ulcerative colitis (ICD-10: K51.0, K51.1, K51.2, K51.3, K51.5, K51.8, K51.9) between January 2010 and December 2021 (incident or prevalent).

8.2.2. Exclusion Criteria

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

1. Age <18 years at the start of tofacitinib use.
2. Use of tofacitinib before reimbursement (01 Mar 2019).
3. < 8 weeks of treatment with tofacitinib at the start of data mining.
4. History of panproctocolectomy, IPAA or ileostomy.

8.3. Variables

The primary variable is the first recording (date) with tofacitinib for the treatment of ulcerative colitis (ICD-10: K51). Additional variables to be collected according to the list in Table 1.

Table 1. Variables Collected in This Study

Data source for all variables is the eDMT based on patient charts.

Variable	Role	Operational definition
Tofacitinib start date	Index Inclusion criteria 1 Exclusion criteria 2	First day on tofacitinib administration
Date of birth	Exclusion criteria 1 Primary objective 7.2.1.a	Age will be defined as of index date
History of bowel surgery	Exclusion criteria 4	Panproctocolectomy, IPAA or ileostomy
Gender	Primary objective 7.2.1.a CCI [redacted]	Male/female
Smoking status	Primary objective 7.2.1.a CCI [redacted]	Current/ex-smoker/non-smoker/unknown
BMI	Primary objective 7.2.1.a CCI [redacted]	Derived from weight and height
Weight	Primary objective 7.2.1.a	kg
Height	Primary objective 7.2.1.a	cm
Treating hospital	Primary objective 7.2.1.a CCI [redacted]	name of treating hospital
Mayo score	Primary objective 7.2.1.c Secondary objectives 7.3.1.b, 7.3.1.c, 7.3.1.d, 7.3.1.e, 7.3.1.f, 7.3.1.i, 7.3.1.j, 7.3.1.k, 7.3.1.l, 7.3.1.o, 7.3.1.p. CCI [redacted]	Sum of "endoscopic findings", "stool frequency", Doctors assessment of disease severity" and "rectal bleeding"
First UC diagnose	Primary objective 7.2.1.b Inclusion criteria 2 CCI [redacted]	Date
Extent of colonic involvement	Primary objective 7.2.1.b CCI [redacted]	Montreal classification: E1, E2 or E3
Endoscopic findings	Primary objective 7.2.1.c and 7.2.1.e. Secondary objective 7.3.1.m CCI [redacted]	0-3 (mayo score component)
Histological activity	Primary objective 7.2.1.e Secondary objective 7.3.1.n CCI [redacted]	Active disease (2) / inactive disease (1) /normal histology (0) / not determined
Clinician's assessment of disease severity	Primary objective 7.2.1.c CCI [redacted]	0-3 (mayo score component)

Variable	Role	Operational definition
Stool frequency	Primary objective 7.2.1.c Secondary objectives 7.3.1.r	0-3 (mayo score component)
Rectal bleeding	Primary objective 7.2.1.c Secondary objective 7.3.1.s	0-3 (mayo score component)
Fecal calprotectin	Primary objective 7.2.1.d, Secondary objectives 7.3.1.g and 7.3.1.h. CCI [redacted]	mg/kg
Plasma CRP	Primary objective 7.2.1.d Secondary objective 7.3.1.t CCI [redacted]	mg/L
Blood hemoglobin	Primary objective 7.2.1.d, Secondary objective 7.3.1.u CCI [redacted]	g/L
Blood leukocytes	Primary objective 7.2.1.d Secondary objective 7.3.1.v CCI [redacted]	cells/L
Blood thrombocytes	Primary objective 7.2.1.d Secondary objective 7.3.1.w CCI [redacted]	cells/L
Blood lymphocytes	Primary objective 7.2.1.d Secondary objective 7.3.1.x CCI [redacted]	cells/L
Blood neutrophiles	Primary objective 7.2.1.d Secondary objective 7.3.1.y CCI [redacted]	cells/L
Plasma albumin	Primary objective 7.2.1.d Secondary objective 7.3.1.z CCI [redacted]	g/L
Tofacitinib dose	Secondary objectives 7.3.1.a, 7.3.1.aa and 7.3.1.bb	mg*times/per day or "not on treatment"
Colectomies	Secondary objective 7.3.1.cc CCI [redacted]	Date
Type of healthcare contact	Secondary objective 7.3.1.cc CCI [redacted]	outpatient visit, remote contact, emergency visit or hospitalization
Prior IBD treatments • corticosteroids • 5-aminosalicylic acid (5-ASA)	Secondary objective 7.3.2 CCI [redacted]	Yes/no (For each treatment)

Variable	Role	Operational definition
• azathioprine • 6-mercaptopurine • methotrexate • cyclosporine • ustekinumab • vedolizumab • adalimumab • infliximab • golimumab		
Concomitant medications • corticosteroids • 5-ASA	Secondary objective 7.3.1.q, CCI [redacted]	product & dose
Extraintestinal manifestations: arthralgia, arthritis, sacroiliitis, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, uveitis, ankylosing spondylitis, aphthous stomatitis, psoriasis	CCI [redacted]	Yes/no per pre-specified list
Prior diagnoses	CCI [redacted]	Yes/no per pre-specified list
Death date or lost to follow up	Used to define end of follow up	Date

Detailed definitions of variables and their analysis is available in the statistical analysis plan (SAP).

8.4. Data Sources

This study relies on a secondary use of existing and available data in patient registers and patient charts in Finland. The data will be gathered from hospital patient information systems. All data in this study is collected from these patient information systems and made available in aggregated form for data-analysis.

8.5. Study Size

This study is an observational study designed to provide mainly descriptive summary information. There are no hypotheses in the study. Hence sample size calculations are not applicable. The objective is to include all patients that have used tofacitinib in UC in Finland. Estimated number of observations is 100-150 subjects to the timing on the data collection.

8.6. Data Management

This study protocol will be evaluated and approved by the Finnish Health and Social Data Permit Authority Findata before any activity starts. Findata will issue permits and deliver the data for this study. Based on the protocol the clinical research organization (CRO) Medaffcon will design an eDMT form which will be provided to Findata. A predefined list of data miners will be submitted to Findata. eDMT form will be provided to data miners by Findata.

Each data miner will have access to a set of patient charts to collect the requested data using protected eDMTs. The eDMT is created and maintained by Granitics Oy. In each hospital district (register holder) the assigned data miner will transfer completed eDMT forms to Findata. Findata will provide the pseudonymized pooled data into a secure analysis environment, maintained by the same authority in a csv, xlsx or comparable format (not eDMT-format). Only a preassigned biostatistician from Medaffcon has access to this multifactor identification protected remote server, and only aggregate-level data can be extracted. Thus, individual patients cannot be identified from this data set.

Medaffcon will analyze the data using the statistical software R (version 3.6.1 or higher). Only aggregate results can be extracted from the Findata analysis environment and be available for evaluation for sponsor. Data will be stored at Findata. Medaffcon will be the study register holder, and analyses will be performed according to the SAP by Medaffcon and Pfizer.

Internal validity will be assured by consulting Finnish clinical experts on data integrity, clinical relevance, and plausibility of the results.

All results of this study will be presented in aggregate level data only, no individual level data can be reported. Any patient groups of less than 5 patients cannot be exported from Findata servers. This means that eg, if two patients smoke, it will be reported as “<5 patients smoke”.

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All analysis will be performed by Medaffcon. In short, patients will be described at baseline using appropriate summary statistics.

All analyses are descriptive of nature, and descriptive statistics and/or illustrations will be reported.

CCI [redacted] Persistence of treatment will be assessed using time-to-event models (namely Kaplan-Meier fit and/or Cox proportional hazards model). Changes in treatment outcomes (vs. baseline) will be assessed using repeated measures longitudinal models. Baseline data may be used as covariates in the models where feasible and appropriate.

All p-values are descriptive in nature, and there are no *a priori* hypotheses to be tested. P-values lower than 0.05 will be considered statistically significant. All statistical tests will be considered hypothesis generating, and any significant results should be validated later.

Statistical interpretation of the results will be validated by Medaffcon statisticians/Data Scientists with relevant degree.

8.8. Quality Control

Medaffcon has an internal quality control (QC)/log documentation used for RWE studies. The document records general data QC (including for example measures for data and variable coverages, number of individuals and data rows, changes as function of time and checks for systematic gaps on data coverage and outliers in the data where appropriate). Additionally, all notes or data processing and definitions, especially any deviations from SAP, will be recorded and later reported. All analyses and data processing will be performed using R, a language and environment for statistical computing and graphics, in R-studio environment. All analysis scripts will be saved, and there is version control and external back-ups for the scripts. At the end of study, all scripts will be archived to assure analysis reproducibility, and plausible later audits (by client and/or from scientific publication side).

All study results will be discussed within Medaffcon and Pfizer teams, and any uncertainties will be further validated by clinical experts and/or wider team of Pfizer and/or Medaffcon RWE experts and Data Scientists where appropriate.

8.9. Limitations of the Research Methods

The main strength of this study is the nation- and patient-wide coverage of the cohort. The study is expected to include all 21 health care districts in Finland. The data is also versatile as it is derived from the patient information systems in the hospital districts.

The main limitation of the study are its' retrospective nature and the expected number of observations (approximately 100 – 150 patients). Therefore, some sub-group or stratified analyses are not necessarily possible. It is also likely that the data is partially incomplete because of the variation between hospitals. All variables or sum variable components are not necessarily available from different electronical health records. Tofacitinib has been used in Finland for a rather short time so data for all endpoints at all timepoints may not be calculated/available. As in the registry studies in general the primary data source (hospital electronic health record [EHR]) in this study may be prone to potential human errors. Data is subject to gaps and human errors made by physicians entering data into the system.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

No waiver was received as this is not applicable. Per the Act on Secondary Use of Health and Social Data 552/2019 (in Finnish: Laki sosiaali- ja terveystietojen toissijaisesta käytöstä), no institutional review board or independent ethics committee for this retrospective registry study is required.

9.4. Ethical conduct of the study

Per the Act on Secondary Use of Health and Social Data 552/2019 (in Finnish: Laki sosiaali- ja terveystietojen toissijaisesta käytöstä), no ethical approval for this retrospective registry study is required. This study protocol will be evaluated and approved by the Finnish Health and Social Data Permit Authority Findata before any activities.

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).[13]

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Secondary Data Collection Study Structured Data Analysis

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The detailed results obtained from this study will be available upon publication. Research results from this study will be published in peer reviewed scientific journals and international scientific congresses. The Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

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 party responsible for collecting data from the participant 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.

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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