NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Active Surveillance, Post-Authorisation Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG)
Protocol number	A3921344
Protocol version identifier	5.0
Date	09 February 2022
EU Post Authorization Study (PAS) register number	EUPAS40131
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-014
Procedure number	EMEA/H/C/004214/X/0005/G
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No

Research question and objectives	**Research Question**: What are the incidence rates of safety events of interest (as described below) in adult ulcerative colitis (UC) patients treated with tofacitinib, as compared to the incidence rates in UC patients treated with other approved systemic agents, and UC patients naïve to biologics and immunomodulators/immunosuppressants? **Primary Objective**: Estimate the incidence rates of malignancy excluding non-melanoma skin cancer (NMSC) and venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]), in adult UC patients who initiate tofacitinib in the course of routine clinical care, as well as UC patients initiating treatment with other approved systemic agents, and UC patients naïve to biologics and immunomodulators/immunosuppressants. **Secondary Objectives**: 1. Estimate the incidence rates of other safety endpoints of interest, including (but not limited to) NMSC, lung cancer, lymphoma, opportunistic infections (e.g., tuberculosis), major adverse cardiac events (MACE), myocardial infarction (MI), serious infections, herpes zoster (HZ), progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, fractures, and all-cause mortality in adult UC patients who initiate tofacitinib in the course of routine clinical care, as well as UC patients initiating treatment with other approved systemic agents, and UC patients naïve to biologics and immunomodulators/immunosuppressants. 2. Estimate - the incidence rates of primary and secondary safety events of interest

	stratified by tofacitinib dose (5mg vs. 10mg dose). 3. Estimate the hazard ratios of the primary and secondary safety events of interest between tofacitinib-treated patients (Cohort 1) and comparator Cohorts 2, 3 and 4 described below, assuming sufficient statistical power. <u>Tofacitinib cohort</u> Cohort 1: UC patients initiating tofacitinib, stratified by prior biologic use (i.e., patients naïve to biologic vs. patients with prior biologic use who are initiating tofacitinib) <u>Primary comparator cohort</u> Cohort 2: UC patients who initiate biologics, with/without concurrent immunomodulators/immunosuppressants, stratified on tumor necrosis factor inhibitor (TNFi)/non-TNFi use and number of previous biologic treatments <u>Secondary comparator cohorts</u> Cohort 3: UC patients who initiate immunomodulators/immunosuppressants without concurrent biologics Cohort 4: UC patients naïve to both biologics and immunomodulators/immunosuppressants
Country(-ies) of study	Sweden
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADD	Average daily dose
AE	Adverse event
AZA	Azathioprine
BID	Bis in die (Twice a day)
CD	Crohn's Disease
CI	Confidence interval
CKD	Chronic kidney disease
CLL	Chronic lymphocytic leukemia
CV	Cardiovascular
CVD	Cardiovascular disease
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EU	European Union
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HR	Hazard ratio
Hx	History
HZ	Herpes zoster
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease - unspecified
ICD	International Classification of Diseases
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IQR	Interquartile range
ISPE	International Society for Pharmacoepidemiology
IR	Incidence rate
IRB	Institutional Review Board
JAK	Janus kinase
MACE	Major adverse cardiovascular events
MAH	Marketing authorization holder
MI	Myocardial Infarction
MTX	Methotrexate
NDA	New Drug Application
NHL	Non-Hodgkin Lymphoma
NI	Non-interventional

Abbreviation	Definition
NMSC	Non-melanoma skin cancer
NSAIDs	Non-steroidal anti-inflammatory drugs
OI	Opportunistic infection
PASS	Post-Authorization Safety Study
PE	Pulmonary embolism
PML	Progressive multifocal leukoencephalopathy
PPI	Proton pump inhibitor
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Patient-years
RMP	Risk management plan
RR	Relative risk
SAP	Statistical analysis plan
SmPC	Summary of product characteristics
SWIBREG	Swedish Quality Register for Inflammatory Bowel Disease
TB	Tuberculosis
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
VTE	Venous thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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Country Coordinating Investigators

Not applicable

4. ABSTRACT

- **Title**: An Active Surveillance, Post-Authorisation Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Real World Setting Using Data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG)

- **Main author/affiliation**: Nana Koram, PhD, MPH, Pfizer, Inc.

- **Rationale and background**: Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the European Union (EU) in July 2018 at a dose of 5mg twice daily or 10mg twice daily for the treatment of adults with moderate-to-severe ulcerative colitis (UC), who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Malignancy excluding non-melanoma skin cancer (NMSC) is an important potential risk and venous thromboembolism (VTE) is an important identified risk associated with the use of tofacitinib, and follow-up of large cohorts of patients over a long period is needed to evaluate the risks of these safety events, as well as other potential safety events of interest, that may be associated with tofacitinib treatment. Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed and unexposed patients using actively collected prospective data included in the SWIBREG register.

- **Research question**: What are the incidence rates of safety events of interest in adult UC patients treated with tofacitinib in routine clinical care, as compared to the incidence rates in UC patients treated with other approved systemic agents, and UC patients naïve to biologics and immunomodulators/immunosuppressants?

- **Objectives**: The primary objective is to estimate the incidence rates of malignancy excluding NMSC, and VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]) in adult UC patients who initiate tofacitinib in the course of routine clinical care, as well as the incidence rates in UC patients treated with other approved systemic agents such as biologics and immunomodulators/immunosuppressants, and in UC patients naïve to biologics and immunomodulators/immunosuppressants.

  There are three secondary objectives:

  1. Estimate the incidence rates of other safety events of interest including (but not limited to) NMSC, opportunistic infections (e.g., tuberculosis), lung cancer, lymphoma, major adverse cardiac events (MACE), myocardial infarction (MI), serious infections, herpes zoster (HZ), progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, fractures, and all-cause mortality in adult UC patients who initiate tofacitinib in the course of routine clinical care, as well as the incidence rates in UC patients initiating treatment with other approved systemic agents such as biologics and immunomodulators/immunosuppressants, and in UC patients naïve to biologics and immunomodulators/immunosuppressants.

2. Estimate the incidence rates of primary and secondary safety events of interest stratified by tofacitinib dose (5mg vs. 10mg twice daily).

3. Estimate the hazard ratios of primary and secondary safety events of interest between tofacitinib-treated patients (Cohort 1) and comparator Cohorts 2, 3 and 4 described below, assuming sufficient statistical power.

Cohort 1 (Tofacitinib cohort): UC patients initiating tofacitinib, stratified by prior biologic use (i.e., patients naïve to biologics vs. patients with prior biologic use who are initiating tofacitinib)

Primary comparator cohort

- Cohort 2 (Biologics cohort): UC patients who initiate biologics, with/without concurrent immunomodulator/immunosuppressants, stratified on TNFi/non-TNFi use and number of previous biologic treatments

Secondary comparator cohorts

- Cohort 3 (Immunomodulators/immunosuppressants cohort): UC patients who initiate immunomodulators/immunosuppressants (i.e., methotrexate [MTX], azathioprine [AZA], mercaptopurine [6-MP]) without concurrent biologics

- Cohort 4 (Naïve cohort): UC patients naïve to both biologics and immunomodulators/immunosuppressants (biologic/immunomodulator/immunosuppressant naïve cohort)

- **Study design**: This is an active surveillance study utilizing data from the existing SWIBREG register, which is an ongoing, prospective, observational, cohort of Swedish patients with inflammatory bowel disease (IBD) with the primary aim of studying the safety of new therapies for IBD during routine post marketing clinical use. This study will focus only on UC patients enrolled in the SWIBREG register.

- **Population**: The study population will include adult UC patients aged ≥18 years enrolled in SWIBREG who are initiating treatment with tofacitinib (Cohort 1) from 01 October 2018 through 31 March 2024. The study will also include the following comparator cohorts: Cohort 2: UC patients who initiate biologics, with/without concurrent immunomodulators/immunosuppressants, stratified on TNFi/non-TNFi use and number of previous biologic treatments; Cohort 3: UC patients who initiate immunomodulators/immunosuppressants without concurrent biologics; Cohort 4: UC patients naïve to both biologics and immunomodulators/immunosuppressants.

  Patients in Cohort 4 are expected to have milder disease compared with patients in the other 3 cohorts, and in particular, compared with patients in the tofacitinb-treated cohort (Cohort 1). Patients in Cohort 3 are also expected to have milder disease compared with patients in Cohorts 1 and 2. Additionally, as per the prescribing recommendations in the Summary of Product Characteristics (SmPC), the majority of patients in Cohort 1 are likely to be patients who have previously failed at least one TNFi therapy prior to receiving tofacitinib, while Cohort 2 is more likely to consist of a balance of both patients

who have previously failed TNFi therapy and patients whose disease is successfully being treated with TNFi therapy.

- **Variables**: The study variables include baseline patient characteristics (i.e., clinical and demographic characteristics, comorbidities, and current and past therapies). The primary outcomes of interest are malignancy excluding NMSC and VTE. Other safety events of interest include (but may not be limited to) the following: NMSC, lung cancer, lymphoma, serious infections, opportunistic infections, MACE, MI, PML, GI perforations, fractures and all-cause mortality.

- **Data sources**: Baseline and follow-up data, including patient demographics, disease characteristics, and treatment will be based on data from SWIBREG and the Swedish Patient and Prescribed Drug Registers. SWIBREG data will be augmented with linkages to the Swedish Cancer, Contagious Diseases, Medical Birth, Causes of Death and Total Population Registers.

- **Study size**: All eligible patients in SWIBREG during the study period will be included, with no upper limit on the sample size. The feasibility of more refined comparative analyses to evaluate safety events of interest that adequately adjust for potential confounders will be assessed in two interim reports and at the end of data collection, and will be based on statistical power, as described below. As such, the comparative analysis is defined as one of the secondary objectives.

  Preliminary power calculations assume a 0% annual rate of switching, a fixed power of 80% at α=0.05, an estimated 1560 UC patients on biologics in Sweden (Pfizer, 2017 internal data), estimated rate in patients on biologics of 7/1000 person-years (PY) for malignancy excluding NMSC, and estimated rate of VTE in UC patients in general in Sweden of 1.97/1000 PY based on published literature, 6-year total study duration (5 years of patient accrual, and a minimum of 12 months follow-up for the last enrolled patient), and a 5% annual loss to follow up in both cohorts. For an event with a rate of 7/1000 PY, such as malignancy, excluding NMSC, sample sizes of 500 to1000 tofacitinib-treated patients would allow for relative risks of 2.27 and 1.93, respectively, to be detected between the tofacitinib and biologics cohorts. For an event with a rate of 1.97/1000 PY, such as VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for relative risks of 3.89 and 3.01, respectively, to be detected between the cohorts. Assuming a 30% annual rate of switching, the detectable relative risks between the tofacitinib and biologic cohorts at 80% power and α= 0.05 are higher (i.e., for malignancy excluding NMSC), sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 6.02 and 4.44, respectively, while for VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 15.51 and 10.28, respectively.

  Based on these estimations, comparative analyses will be performed if there are $\geq$500 patients in the tofacitinib cohort, which would allow for between 2.27 to 15.51 relative risk to be detected with 80% power at the 5% significance level, assuming 0% to 30% annual switching between the tofacitinib and biologic cohorts.

- **Data analysis:** This study will include descriptive summaries of baseline characteristics of the tofacitinib cohort (Cohort 1), biologics cohort (Cohort 2), immunomodulators/immunosuppressants cohort (Cohort 3) and naïve cohort (Cohort 4). Crude incidence rates (with corresponding 95% confidence intervals) of the safety events of interest as specified in the primary and secondary objectives will be estimated for each cohort. If the assumptions listed above are met, incidence rates of the primary and secondary safety events of interest will be compared between the tofacitinib cohort and Cohorts 2, 3 and 4 using propensity score matched multivariable Cox regressions adjusting for sex, age, year of treatment start, disease severity, comorbidities and other potential confounders for more refined evaluation of safety endpoints.

  Several sub-group analyses will also be conducted. Incidence rates of the primary and secondary safety events of interest for the tofacitinib cohort will be stratified by prior biologic use (prior biologic use vs. none; among those with prior biologic use, 1st biologic vs. 2nd biologic vs. ⩾3 biologic); patient age (patients aged ⩾50 years vs. <50 years; patients aged ⩾65 years vs. <65 years), tofacitinib dose, and for the outcome of VTE patients with ⩾1 VTE risk factors vs. no VTE risk factors. For the outcomes of MACE and MI, incidence rates of the safety events of interest for the tofacitinib cohort will be stratified by patients with ≥1 cardiovascular (CV) risk factors vs. no CV risk factors. For the outcome of lymphoma, incidence rates of the safety events of interest for the tofacitinib cohort will be stratified by lymphoma subtypes. If the assumptions listed above are met, comparative assessments between the tofacitinib cohort and comparator cohorts will be conducted, otherwise crude and age-adjusted rates will be presented along with 95% confidence intervals for all four cohorts.

- **Milestones**:

  Start of data collection: March 2021
  End of data collection: March 2026
  Interim report 1: August 2022
  Interim report 2: August 2024
  Final study report: March 2027

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	July 2020	Title page	Protocol version and date updated Research question updated to indicate comparisons between tofacitinib-treated patients and other UC cohorts will be conducted; study objectives updated to include a third secondary objective outlining comparative assessments between the tofacitinib cohort and 3 UC comparator cohorts that will be conducted; replacement of "contextualization" cohorts with comparator cohorts; definition of primary and secondary comparator cohorts; removal of hepatic events and surgery for UC as outcomes of interest; minor editorial changes	Protocol was amended Pharmacovigilance Risk Assessment Committee (PRAC) request and clarifications
	July 2020	Section 2	VTE added to list of abbreviations	Minor editorial change
	July 2020	Section 3	List of principal investigators was updated to remove Michael Sachs and replace him with Jacob Järås	Michael Sachs is no longer affiliated with the study
	July 2020	Section 4	Rationale and background section: Updated to clarify that malignancy excluding non-melanoma skin cancer (NMSC) is an important potential risk and venous thromboembolism (VTE) is an important identified risk Research question and Objectives sections: Research question updated to indicate comparisons between tofacitinib-treated patients and other UC cohorts will be conducted; Addition of a third secondary objective noting that comparative assessments between the tofacitinib cohort and 3 UC comparator cohorts will be conducted; replacement of "contextualization" cohorts with comparator cohorts; definition of primary comparator cohort and secondary comparator cohorts; removal of hepatic events and surgery for UC as outcomes of interest; other minor editorial changes Study design section: Minor editorial change Population section: Updated to include patient accrual period, and to further clarify the defintions of the primary and secondary comparator cohorts	PRAC request and clarifications

			Variables section: Various minor editorial changes Study size: Updated to indicate that comparative analyses will be conducted; sample sizes required to achieve 80% statistical power to detect a relative risk of 2 for incidence rates of primary safety events among tofacitinib-treated patients and comparator cohorts provided Milestones section: Updated to reflect new study timeline	
	July 2020	Section 6	Updated to reflect new study timeline	Editorial changes
	July 2020	Section 7	Updated to clarify that malignancy excluding non-melanoma skin cancer (NMSC) is an important potential risk and venous thromboembolism (VTE) is an important identified risk Updated to clarify that changes to the Summary of Product Characteristics (SmPC) were implemented beginning January 2020 Updated to include prevalence of UC in Sweden	Editorial changes
	July 2020	Section 8	Research question updated to indicate comparisons between tofacitinib-treated patients and other UC cohorts will be conducted; study objectives updated to include a third secondary objective outlining comparative assessments between the tofacitinib cohort and 3 UC comparator cohorts; replacement of "contextualization" cohorts with comparator cohorts; definition of primary comparator cohort and secondary comparator cohorts; other minor editorial changes	PRAC request and clarifications
	July 2020	Section 9.1	Updated to clarify study duration (patient accrual period and minimum amount of follow-up for last enrolled patient); updates to indicate that comparative assessments will be conducted assuming sufficient statistical power	PRAC request and clarifications
	July 2020	Section 9.2	Updated to include prevalence of UC in Sweden	Editorial change
	July 2020	Section 9.2.1 and sub-sections	Updated to include clarify patient accrual period, baseline period, minimum follow-up duration for last enrolled patient; clarifications added to inclusion criteria for tofacitinib	PRAC request and clarifications

			and comparator cohorts; clarification of treatment of patients with concomitant use of tofacitinib with either biologics or potent immunosuppressants/ immunomodulators added; minor editorial changes	
	July 2020	Section 9.2.2	Clarification to specify that patients with history of UC surgery will be excluded from Cohort 4 added	PRAC request
	July 2020	Section 9.3	Updated to clarify that non-demographic baseline variables will be identified via ICD/ATC drug codes	PRAC request
	July 2020	Section 9.3.1 and sub-section	Updated to remove "concomitant" and to clarify that use of immunomodulators/immuno-suppressants and/or biologics at index date, use of immunomodulators/immunosuppressants and/or biologics prior to the index date will be assessed at baseline; subsection added to define VTE risk factors to be assessed	PRAC request and clarifications
	July 2020	Section 9.3.2 and sub-sections	New section (Exposure variables) added to provide more details on exposure measurement (tofacitinib, biologics, and immunomodulators/immunosuppressants will be identified via ATC drug codes through linkages with the Swedish prescribed drug register); new sub-sections included to provide additional details on how duration of exposure will be estimated and tofacitinib dose calculation	PRAC request and clarifications
	July 2020	Section 9.3.3	New section added to provide additional details of index date definitions for all four cohorts	PRAC request and clarifications
	July 2020	Section 9.3.4	Updated to specify that a minimum follow-up duration of 12 months will be allowed for adequate evaluation of safety events; clarification that PML will be assessed using 2 analytic approaches (90-day risk window and "once exposed always at risk") included; minor editorial changes	PRAC request and clarifications
	July 2020	Section 9.3.5	Additional section added to provide details on how medication restarts will be analyzed	PRAC request and clarifications
	July 2020	Section 9.3.6	Removal of hepatic events and surgery for UC as outcomes of interest for the study; discussion of how outcome variables are identified in the various Swedish registers and whether or not the definitions have	PRAC request and clarifications

			been validated has been included; minor editorial changes	
	July 2020	Section 9.5	Updated to include sample size estimations, including (for the primary safety events of interest) sample size of tofacitinib cohort that will be required to achieve 80% statistical power to detect a relative risk of 2 for the incidence rates of events among the tofacitinib and comparator cohorts; minor editorial changes	PRAC request
	July 2020	Section 9.7 and sub-sections	Updated to include several sub-sections detailing the primary and secondary analytic approaches, type of sub-group analyses to be conducted, additional information on comparative assessments and use of propensity score matched multivariable Cox regressions, and information on the planned analyses for the interim and final study reports; minor editorial changes	PRAC request and clarifications
	July 2020	Section 9.9	Updated to clarify the extent to which patients with VTE risk factors can be identified from the Swedish registers; clarifications regarding the limitations associated with the planned comparative analyses; minor editorial changes	PRAC request and clarifications
	July 2020	Section 12	Updated to clarify that as per EMA PASS guidance, publications will be submitted to EMA within 14 days of journal acceptance	Editorial change
	July 2020	Section 13	Additional references added	Editorial changes
	July 2020	Section 14.1, Table 4	Updated to include ICD/ATC drug codes that will be used to identify non-demographic baseline variables; additional updates to include information on whether or not algorithms that will be used to identify study outcomes of interest have been validated; removal of ICD codes for hepatic events and surgery for UC as these are no longer study outcomes of interest	PRAC request and clarifications
	July 2020	Annex 2	Editorial changes	Updated to reflect changes made throughout protocol
2	November 2020	Title page	Protocol version identifier, date and product reference number updated Research question updated to reflect comparative nature of study	Editorial changes and PRAC request and clarifications
	November 2020	Abstract	Research question updated to reflect comparative nature of study	

			Study size, data analysis sections updated to provide updated power and sample size estimations and to clarify comparative analysis plan Milestones (start of data collection) updated	
	November 2020	Section 6	Start of data collection and footnote dates updated	Editorial change
	November 2020	Section 8	Research question updated to reflect comparative nature of study	PRAC request
	November 2020	Section 9.1	Updated to clarify comparative analysis plan	PRAC request and clarification
	November 2020	Section 9.2.1.1	Editorial change	Editorial change
	November 2020	Section 9.3.1.1	Editorial change to footnote	Editorial change
	November 2020	Section 9.3.2.2	Time periods for induction and maintenance for the tofacitinib dose calculation clarified	PRAC request
	November 2020	Section 9.3.4	Editorial change	Editorial change
	November 2020	Section 9.5	Updated to provide sample size estimations and to clarify comparative analysis plan	PRAC request and clarifications
	November 2020	Section 9.7.1	Updated to provide illustration to clarify as-treated approach with the 90-day extension period	PRAC request and clarifications
	November 2020	Section 9.7.3	Sensitivity analysis for acute events moved here from previous section	Editorial change
	November 2020	Section 9.7.4	Clarification to show that subgroup analysis of patients with VTE risk factors will be conducted only for the relevant outcomes of MACE and VTE	PRAC request
	November 2020	Section 9.7.5	Additional detail added to define what is meant by sufficient statistical power	PRAC request and clarifications
	November 2020	Section 9.7.7	Updated to clarify contents of interim reports	PRAC request and clarifications
	November 2020	Section 9.7.8	Updated to clarify contents of final report	PRAC request and clarifications
	November 2020	Section 9.9	Editorial changes, and updates to clarify VTE capture in SWIBREG and impact on study	Editorial changes, and PRAC request and clarifications

	November 2020	Section 12	Editorial change	Editorial change
	November 2020	Section 15	List of tables updated	Editorial changes
3	September 2021	Title page	Updated to replace old Pfizer logo with new one Updated to include EU PAS registration number Updated objectives to include lung cancer, lymphoma, MI and fratures as additional safety endpoints	Editorial changes PRAC request and clarifications
	September 2021	List of Abbreviations	Updated to include new abbreviations	Editorial changes
	September 2021	Abstract	Updated objectives and variables to include lung cancer, lymphoma, and as additional safety endpoints Updated to include fractures as additional safety endpoint Updated analysis to specify subgroup analyses for MACE and MI, as well as for lymphoma subtypes	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk
	September 2021	Section 6	Updated milestone table to include EU PAS registration date	Editorial change
	September 2021	Section 7	Updated to include information on changes to SmPC resulting from 2021 signal evaluation procedure	PRAC request and clarifications
	September 2021	Section 8	Updated objectives to include lung cancer, lymphoma, and MI as additional safety endpoints Updated to include fractures as additional safety endpoint	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk
	September 2021	Section 9.3.1	Baseline variables updated to include history of NMSC, lung cancer, and lymphoma Updated to include fractures as additional safety endpoint	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk
	September 2021	Section 9.3.1.1	Updated to specify CV risk factors	PRAC request and clarifications
	September 2021	Section 9.3.4	Updated to include lung cancer, lymphoma, and MI as additional safety endpoints Updated to include fractures as additional safety endpoint	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk

	September 2021	Section 9.3.6	Updated to include lung cancer, lymphoma, and MI as additional safety endpoints Updated to include fractures as additional safety endpoint	PRAC request and clarifications Based on available data, Pfizer has identified fractures as a potential risk
	September 2021	Section 9.7.4	Updated to specify additional subgroup analyses for malignancies excluding NMSC, lymphoma, MACE and MI	PRAC request and clarifications
	September 2021	Section 9.7.7	Updated to note that crude incidence rates for lymphoma subtypes will also be presented in the interim report	PRAC request and clarifications
	September 2021	Section 9.9	Updated to describe limitations surrounding capture of some CV risk factors, and lymphoma subtypes in Swedish registers	PRAC request and clarifications
	September 2021	Section 14.1, Table 4	Updated to include definitions for additional endpoints	PRAC request and clarifications
	September 2021	Annex 2	Signature date updated	Editorial change
4 (version 5.0)	February 2022	Section 9.3.1.1	Updated list of CV risk factors to include history of chronic kidney disease (CKD) and history of hypercholesterolemia, as well as prescribed lipid-modifying agents.	PRAC request and clarification

6. MILESTONES

Milestone	Planned date
Start of data collection	31 March 2021
End of data collection	31 March 2026
Interim report 1*	31 August 2022
Interim report 2**	31 August 2024
Registration in the EU PAS register	17 March 2021
Final study report***	31 March 2027

*Anticipated to include data 01 October 2018 - 31 December 2020
** Anticipated to include data 01 October 2018 - 31 December 2022
*** Anticipated to include data 01 October 2018 - 31 December 2024

7. RATIONALE AND BACKGROUND

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by chronic inflammation of the gastrointestinal tract, marked by an abnormal immune response. UC is restricted to the colon and affects the mucosa of the gut[1]. As a result of the inflammatory reaction, the intestinal wall is damaged, frequently leading to bloody diarrhea and abdominal pain. A recent study evaluated data from 31 medical centers across Western and Eastern Europe (including Cyprus, Denmark, Faroe Islands, Finland, Greece, Greenland, Iceland, Ireland, Israel, Italy, Portugal, Spain, Sweden, UK, Croatia, Czech Republic, Estonia, Hungary, Lithuania, Moldova, Romania, and Russia), representing a total background population of approximately 10.1 million people, and estimated the annual /incidence of UC in 2010 to be 8.2 per 100,000 European adults and adolescents aged $\geq$15 years. Incidence varied by Western vs. Eastern European region, and also between various regions within certain countries from 2.5 per 100,000 residents of Timis, Romania to 31.8 per 100,000 residents of the Faroe Islands (Denmark[2]). In Sweden, the incidence of UC was reported to be 19.2 per 100,000 in 2007[3].

Regarding the prevalence of UC, estimates for European populations vary widely, from 2.4 per 100,000 persons in Romania to 505 per 100,000 persons in Norway[4]. In Sweden, the prevalence of UC is reported to be 0.35% of the population (350 per 100,000 persons)[5]. The EMA's Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (Committee for Medicinal Products for Human Use [CHMP]/Efficacy Working Party [EWP]/18463/2006 Revision 1), estimates prevalence to be 70 to 500 cases per 100,000 with peak age of onset between 15 and 25 years. In 15% of cases, UC is diagnosed in childhood and may present before school age[6]. Data from multiple countries suggest increasing prevalence over time[4,7].

UC presents significant health and socioeconomic burdens for the individual patient and society[8,9,10]. There is currently no cure for UC[1]. Moderate-to-severe UC often requires treatment with systemic agents, such as glucocorticoids and azathioprine[11], many of which

are associated with infectious, cardiovascular, gastrointestinal and malignant adverse events[12,13]. Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the European Union (EU) in July 2018 at a dose of 5 mg twice daily (BID) or 10 mg BID for the treatment of adults with moderate-to-severe UC, who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Malignancy excluding NMSC is an important potential risk associated with the use of tofacitinib. In January 2020, as a result of a reassessment of the benefit-risk of tofacitinib, the European Commission (EC) approved several revisions to the Summary of Product Characteristics (SmPC), including addition of VTE as an important identified risk associated with the use of tofacitinib. Additionally, in June 2021, as a result of a signal evaluation procedure (EPITT number 19382) to assess the increased incidence rate of major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) in patients treated with rheumatoid arthritis (RA) for tofacitinib, the EMA concluded that myocardial infarction (MI), lung cancer, and lymphoma were important identified risks. Separately, fractures was identified as an important potential risk associated with the use of tofacitinib.

Follow-up of large cohorts of patients over a long period is needed to evaluate the risks of malignancy excluding NMSC and VTE, as well as other safety events of interest that may be associated with tofacitinib treatment. It is important that surveillance also examines the occurrence of other co-morbidities and mortality.

Active surveillance studies can estimate incidence rates of safety events of interest overall and within strata of disease severity, treatment history, and other concomitant therapy. The goal of this active surveillance study using data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) is to assess the risk of malignancy excluding NMSC, VTE, and other safety events of interest in UC patients initiating treatment with tofacitinib in a real world setting. Incidence rates of the same endpoints will be estimated for adult UC patients treated with other approved systemic medications, as well as adult UC patients naïve to both biologics and immunomodulators/immunosuppressants, to provide context to the findings.

This non-interventional active surveillance study is designated as a Post-Authorisation Safety Study (PASS) and is a Risk Management Plan (RMP) Category 3 commitment to the European Medicines Agency (EMA).

8. RESEARCH QUESTION AND OBJECTIVES

The research question for this study is: What are the incidence rates of safety events of interest in adult ulcerative colitis (UC) patients aged ⩾18 years treated with tofacitinib, as compared to the incidence rates in UC patients treated with other approved systemic agents, and UC patients naïve to biologics and immunomodulators/immunosuppressants?

Primary Objective:
The primary objective is to estimate the incidence rates of malignancy, excluding NMSC and VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]) among adult UC

patients aged ⩾18 years who initiate tofacitinib in the course of routine clinical care, as well as the incidence rates in UC patients treated with other approved systemic agents such as biologics and immunomodulators/immunosuppressants, and in UC patients naïve to biologics and immunomodulators/immunosuppressants.

Secondary Objectives:

There are three secondary objectives:

1. Estimate the incidence rates of other safety events of interest among adult UC patients aged ⩾18 years who initiate tofacitinib in the course of routine clinical care, as well as the incidence rates in UC patients treated with other approved systemic agents such as biologics and immunomodulators/immunosuppressants, and in UC patients naïve to biologics and immunomodulators/immunosuppressants. These other safety events include (but may not be limited to) the following:

- NMSC
- Lung cancer
- Lymphoma
- Serious infections
- Opportunistic infections (e.g., tuberculosis)
- Herpes zoster (HZ)
- Major adverse cardiac events (MACE)
- Myocardial infarction (MI)
- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Fractures
- All-cause mortality

2. Estimate the incidence rates of the primary and secondary safety events of interest stratified by tofacitinib dose (i.e., 5mg vs. 10mg twice daily).

3. Estimate the hazard ratios of the primary and secondary safety events of interest between tofacitinib-treated patients (Cohort 1) and comparator Cohorts 2, 3, and 4 described below, assuming sufficient statistical power.

- Cohort 1 (Tofacitinib cohort): UC patients initiating tofacitinib, stratified by prior biologic use (i.e., patients naïve to biologic vs. patients with prior biologic use who are initiating tofacitinib)

Primary comparator cohort

- Cohort 2 (Biologics cohort): UC patients who initiate biologics, with/without concurrent immunomodulators/immunosuppressants, stratified on TNFi/non-TNFi use and number of previous biologic treatments

Secondary comparator cohorts

- Cohort 3 (Immunomodulators/immunosuppressants cohort): UC patients who initiate immunomodulators/immunosuppressants (i.e., methotrexate [MTX], azathioprine [AZA], mercaptopurine [6-MP]) without biologics

- Cohort 4 (Naïve cohort): UC patients naïve to both biologics and immunomodulators/immunosuppressants (biologic/immunomodulator/immunosuppressant naïve cohort)

9. RESEARCH METHODS

9.1. Study design

This is a 6-year active surveillance, secondary data collection study of adult UC patients aged ⩾18 years using data in SWIBREG linked via unique patient identifiers[14] to existing nationwide health registers (the prescribed drug register[15], the cause of death register[16], the cancer register[17], the patient register[18] [both the inpatient and outpatient portion] as well as registers of immigration, emigration, vital status, socioeconomic position[19], and place of residence[20]). Due to a one-year lag associated with linking SWIBREG to other Swedish national registers (essential for the assessment of safety events associated with UC therapy), and to allow for a minimum follow-up duration of 12 months, UC patients meeting the study entry criteria through 31 March 2024 will be included in the analysis, follow-up of patients for the study will end 31 March 2025, and end of data collection will be 31 March 2026 when the full dataset with completed linkages will be available for analysis (Section 6).

Incidence rates and associated 95% confidence intervals (CIs) of the safety events of interest will be calculated in all four cohorts. Data capture and follow-up methods are the same for all four cohorts within the Swedish Registers. For both primary and secondary safety events of interest, comparative analyses will be conducted as described in Section 9.7.

9.2. Setting

Sweden is a Scandinavian country with 10 million residents. The prevalence of UC is reported to be 0.35% of the population[5] (about 35,000 patients total). Healthcare is publicly funded, and prescription drugs are provided free of charge above an annual threshold of approximately $250 USD. Patients with UC are typically treated by gastroenterologists, the vast majority of whom work in public and hospital-based clinics[9]. Health and demographic information is recorded in a series of registers with a very high degree of completeness resulting from the mandatory and semi-automated registration. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born thereafter, linkage of data from different registers is possible[14,24]. The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare *(Socialstyrelsen)* and Statistics Sweden (*SCB*), who may perform data linkages and provide de-identified data for research purposes. All patients who are to be included in this study are registered in SWIBREG. The linkage of this registry to other relevant nationwide registers enables monitoring of existing IBD therapies, as they are used in clinical practice.

9.2.1. Inclusion criteria

The active surveillance population includes adult UC patients aged ≥18 years enrolled in SWIBREG who are newly treated with tofacitinib following EMA approval and Swedish launch of the product (product fully available since 01 October 2018) through 31 March 2024. The study will also include three comparator UC cohorts as defined below. Patients in all four cohorts must have a minimum of 12 months of medical history available either in SWIBREG or the other Swedish national registers (data sources described in Section 9.4) prior to the index date (as defined in Section 9.3.3 to allow for adequate capture of baseline variables (Section 9.3.1). Additionally, a minimum follow-up duration of 12 months will be allowed for evaluation of safety events of interest.

9.2.1.1. Cohort 1 (Tofacitinib cohort): Adult UC Patients Initiating Treatment with Tofacitinib

1. Initiation of tofacitinib (i.e., first ever prescription) as captured in SWIBREG from 01 October 2018 through to 31 March 2024 (or if date of first tofacitinib prescription is missing/unavailable in SWIBREG, then as captured in the Prescribed Drug Register).

2. Patients with ⩾1 of any of the ICD-10 codes for IBD in the patient register (diagnosis made in a department of gastroenterology or internal medicine) in combination with ⩾1 record of UC in SWIBREG on or before initiation of tofacitinib treatment.

3. Patients must not have any records of Crohn's Disease (CD) or IBD unspecified (IBD-U) in SWIBREG between the last UC diagnosis and index date [i.e., date of first prescription for tofacitinib].

As per the SmPC, concomitant use of tofacitinib with either biologics or potent immunosuppressants/immunomodulators such as azathioprine, 6-mercaptopurine, ciclosporine and tacrolimus should be avoided. For this study, in the rare instance that concomitant use occurs, follow-up time will be censored and such patients will either be excluded from all cohorts, or if there is an unexpectedly large number of patients in this category, exposures will be assigned to all relevant groups to avoid significant impacts on sample size. In the case of the latter scenario, a sub-group analysis to compare incidence rates of safety events among patients with vs. without concomitant therapy will be conducted. Additionally exposure time for patients with simultaneous use of tofacitinib and a biologic concomitantly, should it occur, will be assigned to the tofacitinib cohort.

9.2.1.2. Cohort 2 (Biologics cohort): Adult UC Patients Initiating Treatment with Biologics with/without concurrent immunomodulators/immunosuppressants

1. Initiation (i.e., first prescription) of a specific biologic agent (any TNFi or non-TNFi agent) as captured in SWIBREG from 01 October 2018 through to 31 March 2024, or in the Prescribed Drug Register (for primarily non-infusion biologic agents) and the patient register (for primarily infusion biologic agents such as vedolizumab).

2. No prior use of the specific biologic agent prior to index date using all available data.

3. Patients with ⩾1 of any of the ICD-10 codes for IBD in the Patient register (diagnosis made in a department of gastroenterology or internal medicine) in combination with ⩾1 record of UC in SWIBREG on or before start of follow-up

4. Patients must not have any records of CD or IBD-U in SWIBREG between the last UC diagnosis and index date [i.e., date of first prescription for specific biologic agent].

Patients in this cohort may also be on immunomodulators/immunosuppressants concurrently.

9.2.1.3. Cohort 3: (Immunomodulators/immunosuppressants cohort): Adult UC Patients Initiating Treatment with Immunomodulators/Immunosuppressants without concurrent Biologics

1. Initiation (i.e., first prescription) of a specific immunomodulator/immunosuppressant agent (without concurrent biologic therapy) as captured in SWIBREG from 01 October 2018 through to 31 March 2024 or in the Prescribed Drug Register.

2. No prior use of the specific immunomodulator/immunosuppressant prior to index date using all available data.

3. Patients with ⩾1 of any of the ICD-10 codes for IBD in the patient register (diagnosis made in a department of gastroenterology or internal medicine) in combination with ⩾1 record of UC in SWIBREG on or before start of follow-up.

4. Patients must not have any records of CD or IBD-U in SWIBREG between the last UC diagnosis and index date [date of first prescription for an immunomodulator/immunosuppressant].

9.2.1.4. Cohort 4 (Naïve cohort): Biologic/immunomodulator/immunosuppressant-naïve Cohort

1. Naïve to biologics/immunomodulators/immunosuppressants/tofacitinib using all available data.

2. Patients with ⩾1 of any of the ICD-10 codes for IBD in the patient register (diagnosis made in a department of gastroenterology or internal medicine) in combination with ⩾1 record of UC in SWIBREG on or before start of follow-up.

3. Patients must not have any records of CD or IBD-U in SWIBREG between the last UC diagnosis and index date as defined in Section 9.3.3.

4. Patients diagnosed with UC since 01 October 2018 through to 31 March 2024.

Patients in this cohort can include patients who are steroid-naïve (e.g., patients treated only with 5-aminosalicylic acid [5-ASA]), patients who are steroid responsive (i.e., patients who

receive intermittent courses of steroids), as well as patients not receiving any prescribed medications for the treatment of their disease.

Overall, patients in Cohorts 2, 3 and 4 are expected to have less severe disease compared with tofacitinib-treated patients and may not be adequate comparator cohorts (limitations discussed in Section 9.9); however they are included here due to the lack of other appropriate comparators. In particular, patients in Cohort 4 are expected to have milder disease relative to patients in the other 3 cohorts, while patients in Cohort 3 are expected to also have milder disease compared with patients in Cohorts 1 and 2. Additionally, as per the prescribing recommendations in the SmPC, the majority of patients in Cohort 1 are likely to be patients who have previously failed TNFi therapy prior to receiving tofacitinib, while Cohort 2 is more likely to consist of a balance of both patients who have previously failed TNFi therapy and patients whose disease is successfully being treated with TNFi therapy.

9.2.2. Exclusion criteria

Patients not meeting the inclusion criteria for any of the respective cohorts will be excluded. Additionally, for Cohort 4, patients with a history of surgery for UC will be excluded, as surgery suggests more severe disease, and such patients would not be representative of patients with generally mild disease in Cohort 4.

9.3. Variables

9.3.1. Baseline Variables

ICD codes and/or ATC drug codes will be used to identify non-demographic baseline variables (Table 4). The baseline period for all cohorts will be the 12 months prior to index date (as defined in Section 9.3.4). Baseline data considered include, but are not restricted to, the following: age, sex, age of UC onset/years since diagnosis, comorbidities within 12 months of the index date for non-malignancy events (e.g., history of serious infection, history of opportunistic infection, history of herpes zoster, history of VTE, history of diabetes mellitus, history of myocardial infarction [MI], history of hypertension, history of fractures), and ever for malignancy events (i.e., history of malignancies excluding NMSC, and specifically history of NMSC, history of lymphoma and history of lung cancer), use of immunomodulators/immunosuppressants or biologics at index date, use of immunomodulators/immunosuppressants or biologics prior to the index date, use of the following medications 12 months prior to the index date: hormonal therapy and contraceptives, oral steroids, oral nonsteroidal anti-inflammatory drugs [NSAIDs], antimicrobials, anticoagulants, beta blockers, bisphosphonates, narcotics, proton pump inhibitors [PPIs] and statins.

9.3.1.1. VTE and CV risk factors

To facilitate the evaluation of the primary endpoint of VTE, the following VTE risk factors will be evaluated at baseline and/or, for some risk factors, within specific time periods prior to index date (Section 9.3.3) as specified below:

- Age
- Previous VTE

- Undergoing major surgery from date of hospital admission to one month after date of discharge
- MI within previous 3 months prior to index date (defined in Section 9.3.3)
- Heart failure
- Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date
- Malignancy
- Diabetes
- Hypertension
- Inherited coagulation disorders
- Inpatient care because of UC (i.e., UC as main diagnostic listing; from date of admission to date after discharge[21])[1]

Other VTE risk factors such as immobilisation, smoking status, and obesity cannot be adequately captured within the Swedish registers, and thus will limit the assessment of this primary endpoint (limitations discussed in Section 9.9). Additionally, previous VTE and new VTE can only be distinguished in the Swedish registers if they are at least 12 months apart (i.e., previous VTE and new VTE that are less than 12 months apart cannot be distinguished) and this will further limit VTE assessment as discussed in Section 9.9.

To facilitate the evaluation of the safety endpoints of MACE and MI, the following CV risk factors will be evaluated at baseline:

- Age (patients ≥65 years vs. <65 years)
- Sex
- History of chronic kidney disease
- History of hypercholesterolemia and prescribed lipid-modifying agents
- History of diabetes
- History of hypertension
- History of previous MI
- History of coronary heart disease
- History of stable angina pectoris
- History of coronary artery procedures

Other CV risk factors such as smoking status, baseline total cholesterol/ high-density lipoprotein (HDL) ratio >4 cannot be adequately captured within the Swedish registers, and

[1] Patients hospitalized due to acute colitis would be at an increased risk for VTE due to multiple factors, including immobilization, and according to consensus guidelines, such patients are recommended to be given thromboprophylaxis in the absence of contraindications. Patients in Sweden receive anticoagulants such as heparin as standard practice.

thus will limit the assessment of the MACE and MI endpoints (limitations discussed in Section 9.9).

9.3.2. Exposure variables

Exposure to tofacitinib, biologics, and immunomodulators/immunosuppressants will be identified via ATC drug codes through linkages with the Swedish prescribed drug register (Section 9.4.2).

9.3.2.1. Duration of exposure

Duration of exposure will be defined based on consecutive prescriptions observed between a patient's index date and 90 days after the prescribed supply is scheduled to be finished. As a sensitivity analysis, an additional 30 days after the prescribed supply is scheduled to be finished will also be included in the duration of exposure.

9.3.2.2. Tofacitinib dose calculation

As per the current SmPC, tofacitinib use in UC patients consists of an induction and maintenance phase, with dosage varying depending on phase. During induction treatment, the recommended dose is 10mg BID for 8 weeks and then 5mg BID for maintenance. However, the induction dose of 10mg BID may be extended for an additional 8 weeks if an adequate therapeutic benefit has not been achieved (16 weeks total), followed by 5mg BID for maintenance. For patients who have failed at least one biologic therapy and lost response to 5mg BID, 10mg BID can be considered for maintenance therapy, although this treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available.

For UC patients who are not at increased risk for VTE, the 10mg BID dose may be considered if the patient experiences a decrease in response on 5mg BID dose, and failed to respond to alternative treatment options for UC such as biologics. The tofacitinib 10 mg BID dose for maintenance treatment must be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used.

To allow for a subgroup of analysis of safety events stratified by tofacitinib maintenance dose, the following time intervals will be used to distinguish between induction and maintenance periods:

Time period 1: Induction period

- Week 1 through Week 8 (from Day 1 to Day 56);

Time period 2: Mixed induction/maintenance period

- Week 9 through Week 16 (from Day 57 to Day 112);

As per the SmPC, maintenance can begin at either the end of Week 8 or at the end of Week 16 so this time period will be a mix of induction and maintenance, and it would not be possible to distinguish between the two treatment phases in the Swedish registers.

Time period 3: Maintenance period

- ≥Week 17 (≥Day 113)

Additionally, average daily dose (ADD) will be estimated using daily defined dose (DDD) via linkages to the prescribed drug register (Section 9.4.2).

For time periods 2 and 3, ADD will be reported as a continuous and categorical variable:

- >5 mg to 11 mg ADD;
- >11 mg to 15 mg ADD;
- >15 to 20 mg ADD; and
- >20 mg ADD.

Patients on 5 mg BID maintenance dose will likely fall within the first 2 dosing categories, while it is expected that patients on the 10 mg BID maintenance dose will fall within the last 2 dosing categories. For time periods 2 and 3, incidence rates of safety events of interest will be further stratified by the dosing categories above to allow for evaluation of patients on the 10 mg BID maintenance dose.

9.3.3. Index date

Index date will be defined as follows:

Cohort 1: This will be the date of first prescription for tofacitinib since 01 October 2018, following a diagnosis of UC as described in Section 9.2.1.1.

Cohort 2: This will be the date of first prescription for a specific biologic agent since 01 October 2018, following diagnosis of UC as described in Section 9.2.1.2. For patients with more than one biologic initiation, more than one index date will be defined (e.g., one for each biologic initiation).

Cohort 3: This will be the date of first prescription for a specific immunomodulator/immunosuppressant agent since 01 October 2018, following diagnosis of UC as described in Section 9.2.1.3. For patients with more than one immunomodulator/immunosuppressant initiation, more than one index date will be defined.

Cohort 4: This will be the date of UC diagnosis as described in Section 9.2.1.4, since 01 October 2018.

9.3.4. Follow-Up

For a given safety event of interest, each patient will be followed from his/her index date as described above until first occurrence of that safety event of interest, treatment switch or discontinuation, with the appropriate outcome-specific extension to exposure (i.e., 90 day window for acute events, and "once-exposed always at risk" approach for non-acute events like malignancy as described below), and with death and emigration from Sweden, and end of data collection treated as censoring events. A minimum follow-up duration of 12 months will be allowed for adequate evaluation of safety events. Patients may switch between treatment cohorts over time. Additionally, patients will be eligible for entry into a particular cohort each time they start a new therapy within the same drug class.

Acute events are thought to potentially occur at a higher rate while on drug, but that increased risk subsides after the drug is discontinued (i.e., serious and opportunistic infections, herpes zoster, MACE, MI, VTE, GI perforation and fractures). These events will be evaluated over a risk window that includes time from drug initiation until 90 days after end of treatment. When a patient initiates a new therapy within the 90-day extension, the time and events during the overlapping period will be assigned to both treatments. The 90-day extension period is implemented in part to accommodate ongoing exposure to treatments with longer half-lives, and in part to ensure that any subclinical or undiagnosed illness at time of end of treatment is captured.

For NMSC, lung cancer, lymphoma and malignancies excluding NMSC, and all-cause mortality, the occurrence of which is expected to be delayed relative to the time of exposure, the outcomes will be evaluated from drug initiation until the first event, loss to follow up or study end, reflecting a "once-exposed always at risk" paradigm. If a patient switches to a new drug, the subsequent observation time will contribute to multiple therapies.

For PML, both the 90-day risk window and the "once-exposed always at risk" approach will be applied.

Additional details related to the analyses using the 90-day risk window and the "once-exposed always at risk" approaches are discussed in Section 9.7 and its sub-sections.

9.3.5. Medication restarts

During the course of follow-up, due to the observational nature of the study, patients may stop and restart medications at the discretion of their physician. Under the "once-exposed always at risk approach", safety events such as malignancy and death will not be affected (i.e., as this approach considers ever-exposure versus never-exposure, no new index dates will be assigned if patients discontinue and restart the same medication, and accrual of patient-time will continue within the same exposure group).

However, treatment episodes that include medication restarts will affect the analysis of non-malignancy events such as serious infections. Patients restarting medications may have a different risk for study endpoints relative to patients who initiate or continue treatment. Therefore, patient characteristics and incidence rates of safety events will be compared for those who restart medications and those who do not, to determine if it is appropriate to

include both types of patients in the same analysis. If no significant difference exists between these groups, all treatment episodes will be analyzed together using the following analytic approach:

- If a medication restart occurs within the 90-day risk window, a new index date will not be assigned and accrual of person-time will continue within the same exposure group.
- If a restart occurs outside of the 90-day risk window, the patient will receive a new index date.

If the data do not support analyzing all treatment episodes together, patients restarting medication will be examined separately.

9.3.6. Outcome Variables

ICD-code based algorithms will be used to identify outcomes in the Swedish Patient Register (Table 4; serious infections, opportunistic infections, herpes zoster, MACE, MI, VTE, PML, GI perforations and fractures), in the Swedish Cancer Register (malignancy excluding NMSC, NMSC, lung cancer and lymphoma), in the Swedish Causes of Death Register (all-cause mortality), and the Swedish national register for contagious diseases (tuberculosis) for which there is a mandatory registration in Sweden. Additional information on the data sources to be used are provided in Section 9.4.

The specific algorithms for defining these outcome variables have not been validated, though the Swedish patient register has been validated several times[18]. The overall positive predictive value (PPV) of the inpatient diagnoses generally ranged from 85% to 95%.

For all-cause mortality, there is an overall 77% agreement between the cause of death from death certificates (on which data in the cause of death register is based) and the cause of death expected based on case summaries. Agreement is higher in younger age groups (98% and 91% agreement in age groups 0–44 years and 45–64 years, respectively) and for some diagnostic groups. For example, there is higher agreement among deceased with malignant neoplasms as the underlying cause of death. Overall, 86% concordance between medical records and the cause of death register was reported for prostate cancer (increasing to 96% in those who died younger than 60 years old), and a similar level of agreement has been reported for cardiovascular disease deaths at a high level of classification (ICD-10 codes at the three digit level)[16].

The definition of MACE has previously been validated in a Swedish early rheumatoid arthritis cohort, with a positive predictive value of 95%. Additionally, a regional validation study of hospitalized acute MI and stroke (components of the MACE endpoint) found positive predictive values of 96% and 94% respectively, in the period 1977 to 1987[22]. An ICD 9 code based algorithm applied to inpatient diagnoses of GI perforations in the US demonstrated high PPV (89.1-100%)[23]. While the ICD algorithms used to define the outcomes of interest may not be validated, their use can be justified given the importance to contextualize the study results with historical findings.

The study outcome variables (defined in Section 14.1) include the following (but may not be limited to):

- Malignancy excluding NMSC
- VTE (DVT and PE)
- NMSC
- Lung cancer
- Lymphoma
- Serious infections
- Opportunistic infections (e.g., tuberculosis)
- HZ
- MACE
- MI
- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Fractures
- All-cause mortality

This list may be extended with a reasonable number of additional sub-diagnoses or new health-related outcomes as agreed to by SWIBREG researchers and Sponsor before the interim reports and final study report. These decisions will be made prior to initiation of analyses and documented in a statistical analysis plan (SAP) kept on file by the Sponsor.

In addition, the final study report will include the number of tofacitinib-exposed pregnancies.

9.4. Data sources

9.4.1. SWIBREG

The Swedish Quality Register for patients with IBD (SWIBREG), including UC, is a structured collection of personal data that was initiated with the purpose to systematically and continuously develop and safeguard quality of Swedish IBD care. In SWIBREG, personal data have been collected from most Swedish IBD caregivers since 2005 and will continue enrolling patients through at least 2025. The data in SWIBREG allow for analysis of safety of IBD treatments over a long follow-up period. Safety events are not routinely collected in SWIBREG, but through linkage to other nationwide healthcare registers (national patient register, cancer register, cause of death register, contagious disease register, medical birth register, and the total population register) all censoring events and safety endpoints of interest can be captured. Additionally, the prescribed drug register allows for prescription confirmation.

In addition to data on safety outcomes and baseline comorbidities or disease history, SWIBREG is also the source of UC patients naïve to biologics/immunomodulators/immunosuppressants agents.

9.4.2. The Patient Register and the Prescribed Drug Register

The Swedish Patient Register provides information on all hospitalized (inpatient treated) patients, and all visits to non-primary outpatient care (such as a visit to a gastroenterologist). Diagnoses are assigned by the physician, as well as date of discharge and discharging hospital for inpatient care, and hospital department. Diagnoses are coded according to the

International Classification of Diseases (ICD), with version 8 used until 1986, version 9 1987 to 1996 and ICD10 since 1997.

The Prescribed Drug Register provides all filled prescriptions in Sweden from 01 July 2005, and may be used to aid correct classification of patients by their history of retrieved IBD therapies, or to define subcohorts based on switches in treatment.

9.4.3. The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and provides data on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/histology. About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%[17].

9.4.4. The Contagious Disease Register

The Contagious Disease Register, since 1971, provides events reported according to the Communicable Diseases Act and the Communicable Diseases Ordinance on diseases that have mandatory reporting in Sweden.

9.4.5. The Medical Birth Register

The Medical Birth Register contains prospectively provided data from antenatal, obstetric, and neonatal records since 1973, and covers all live and still births (but not all miscarriages) in Sweden[25]. Among the variables collected are maternal age, parity, smoking and family situation in early pregnancy, and the infant's birth weight and length, gestational age (primarily based on ultrasound dating), and Apgar score. Complications and mother's and infant's morbidities are coded according to the ICD, with version 8 used until 1986, version 9 1987 to 1996 and ICD10 since 1997.

9.4.6. The Cause of Death Register

The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. Although the register was started in 1952, the data are considered complete since 1961[16].

9.4.7. The Total Population Register

The Total Population Register lists data on residency at a given point in time since it was founded in 1961, and dates of emigration/immigration for all subjects ever resident in Sweden since 1961[20]. This register thus provides information on censoring (death and emigration) of patients[20].

9.5. Study size

The primary analysis is descriptive and all eligible patients in SWIBREG during the study period will be included, with no upper limit on the sample size. Preliminary analysis of data in the Swedish nationwide registers (Section 9.4) indicate that as of 30 June 2020, there were approximately 2600 adult UC patients aged ≥18 years being treated with systemic agents

such as biologics and other immunomodulators/immunosuppressants. Additionally, in a 2017 analysis of data from the Swedish registers, there were approximately 1560 adult patients with moderate-to-severe UC initiating treatment with biologics specifically (both TNFi and non-TNFi).

The feasibility of more refined comparative analyses to evaluate safety endpoints that adequately adjust for potential confounders will be assessed in the interim reports, and at study end will be based on statistical power as described below. Since the comparator cohorts are expected to be a magnitude larger than the tofacitinib-treated cohort, statistical power will be limited by the uptake of tofacitinib (which is difficult to estimate a priori), as well as the ability to find "matchable" patients in the comparator cohorts. Preliminary assessment of the Swedish national registers indicate that as of 30 June 2020, there were approximately 65 adult UC patients aged ≥18 years treated with tofacitinib.

While the primary objective of the study is active surveillance, conducting quantitative, confounding-controlled comparisons will depend on having a sufficient sample size.

In Table 1 and Table 2 below, assuming 500 and 1000 patients exposed to tofacitinib, the relative risk between cohorts that could be detected with at least 80% power at the 5% significance level are summarized. Based on the estimates presented in Table 1, assuming 0% annual rate of switching from tofacitinib to biologic, and 0% annual rate of switching from biologic to tofacitinib, for an event with a rate of 7/1000 PY, such as malignancy, excluding NMSC, a sample sizes of 500 and 1000 tofacitinib-treated patients would allow for relative risks of 2.27 and 1.93, respectively, to be detected between the tofacitinib and biologics cohorts. For an event with a rate of 1.97/1000 PY, such as VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for relative risks of 3.89 and 3.01, respectively, to be detected between the cohorts.

In Table 2, assuming a 30% annual rate of switching, the detectable relative risks between the tofacitinib and biologic cohorts at 80% power and $\alpha = 0.05$ are higher (i.e., for malignancy excluding NMSC), sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 6.02 and 4.44, respectively, while for VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 15.51 and 10.28, respectively.

Based on these estimations, comparative analyses will be performed if there are ≥500 patients in the tofacitinib cohort, which would allow for between 2.27 to 15.51 relative risk to be detected with 80% power at the 5% significance level, assuming 0% to 30% annual switching between tofacitinib and biologic cohorts.

All sample size calculations were conducted using PASS software version 15.0.8, with Logrank test.

Assumptions

- $\alpha=0.05$
- Power=0.8

- Estimated number of ulcerative colitis (UC) patients on biologics in Sweden: n=1560 based on previous analysis using Swedish national registers (Pfizer, internal data)
- 2 different tofacitinib treated patient population sizes: n=500, n=1000
- Estimated rate of malignancy excluding NMSC while on biologic of 7/1000 PY based on previous analysis using Swedish national registers (Pfizer, internal data); Estimated rate of VTE in UC patients in general in Sweden 1.97/1000 PY[36]
- 6-year total study duration (5 years patient accrual, and minimum one-year follow-up for last enrolled patient)
- Constant rate of accrual
- 5% annual loss to follow up among tofacitinib treated patients, and 5% annual loss to follow up among biologic-treated patients.

Table 1. Assuming 0% annual rate of switching from tofacitinib to biologic, and 0% annual rate of switching from biologic to tofacitinib

Table 1. Detectable Relative Risk Among Tofacitinib-Exposed Patients Compared with Biologic-Treated Register Patients with 80% Power, alpha = 0.05, 6-year Study with 5 Years Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, by Safety Event and Tofacitinib Sample Size

Number tofacitinib-treated patients	Estimated rates of safety event while on biologic	Statistical Power	Detectable RR (at 5% significance level)
	Malignancy excluding NMSC		
500	7/1000 PY	80%	2.27
1000	7/1000 PY	80%	1.93
	VTE		
500	1.97/1000 PY	80%	3.89
1000	1.97/1000 PY	80%	3.01

RR = relative risk

Table 2. Assuming 30% annual rate of switching from tofacitinib to biologic, 30% annual rate of switching from biologic to tofacitinib

Table 2. Detectable Relative Risk Among Tofacitinib-Exposed Patients Compared with Biologic-Treated Register Patients with 80% Power, alpha = 0.05, 6-year Study With 5 Years Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, by Safety Event and Tofacitinib Sample Size

Number tofacitinib-treated patients	Estimated rates of safety event while on biologic	Statistical Power	Detectable RR (at 5% significance level)
	Malignancy excluding NMSC		
500	7/1000 PY	80%	6.02
1000	7/1000 PY	80%	4.44
	VTE		
500	1.97/1000 PY	80%	15.51

Table 2. Detectable Relative Risk Among Tofacitinib-Exposed Patients Compared with Biologic-Treated Register Patients with 80% Power, alpha = 0.05, 6-year Study With 5 Years Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, by Safety Event and Tofacitinib Sample Size

Number tofacitinib-treated patients	Estimated rates of safety event while on biologic	Statistical Power	Detectable RR (at 5% significance level)
1000	1.97/1000 PY	80%	10.28

RR = relative risk

9.6. Data management

This study analyzes data consisting of the ongoing SWIBREG register linked to other nationwide registers. The study researchers are responsible for the data management of this study, which will follow the process outlined below:

1. At end of study follow-up (or data cut-off point for interim reports), data will be ordered from SWIBREG and the Swedish Board of Health and Welfare.
2. The data provider of SWIBREG (Health Solutions) will export quality register data to the Board of Health and Welfare.
3. The Board of Health and Welfare will create a study cohort, consisting of all included patients and send the list of their personal identification numbers to Statistics Sweden.
4. A list of all study participants will be sent back to the Board of Health and Welfare and there the study population will be linked to all the health registers.
5. A pseudoanonymized dataset consisting of all UC patients will be sent to the study researchers at Karolinska Institutet (KI). The key to the dataset will be kept at the Board of Health and Welfare, which makes updates to the dataset possible in the future but identification of individual patients impossible for the researchers.

   The dataset will be kept on a secure server and access to the data will be limited to researchers at KI in Sweden analyzing the data.

9.7. Data analysis

Baseline demographic and clinical characteristics for each cohort, including proportion of patients with $\geqslant$1 VTE risk factors will be described. The general analytic approach will be descriptive. For all the safety events of interest, descriptive statistics, counts and proportions, unadjusted cumulative incidence proportions, and crude incidence rates (i.e., number of events per person-years) and age/sex standardized incidence rates with associated two-sided 95% confidence intervals will be calculated as appropriate.

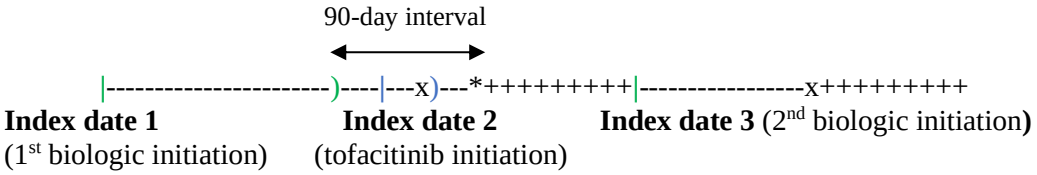
The summary of event rates will be based on survival analysis of time to first event based on an index date defined for each cohort with appropriate censoring rules applied for those who do not experience an event by end of follow-up period (i.e., as described in Section 9.3.4, for a given safety event of interest, patients will be followed from index date until first occurrence of that safety event of interest, treatment switch or discontinuation, with the

appropriate outcome-specific extension to exposure depending on type of event [as described below], and with death and emigration from Sweden, and end of data collection treated as censoring events). Rates will be expressed as events/1000 person-years of follow-up.

9.7.1. Primary analytic approach for acute safety events

For acute safety events of interest, an “as-treated” approach will be used, and person-time will accrue based on the treatment received and will reflect actual confirmed use during each treatment episode. As described in Section 9.3.4, a risk window that includes time from drug initiation until 90 days after end of treatment will also be applied. During this window, patients will continue to accrue “time at risk” for 90 days after the treatment is discontinued. If a new therapy is initiated within the 90-day extension period, the time and events during the overlapping period will be assigned to both treatments. An example of the as-treated approach with the 90-day extension period is provided in the scenario illustrated below.

-------- represents risk period counted
+++++ represents time not included in the risk period
x represents occurrence of an acute safety event of interest such as MACE
) represents drug discontinuation
| represents tofacitinib initiation
| represents biologic initiation
)-----* represents 90-day extension period



In the above scenario, the patient has two biologic initiations and a tofacitinib initiation. The initiation of tofacitinib therapy occurs within the 90-day extension period for the first biologic. Thus, the time and event during the overlapping period will be assigned to both the first biologic and tofacitinib. Specifically, for the first biologic initiation, a safety event occurred within the 90-day extension period, and exposure time is counted from the time of drug initiation (Index date 1) until the occurrence of the safety event. For the tofacitinib initiation, one safety event occurred and exposure time is counted from Index date 2 (date of initiation of tofacitinib which occurs within the 90-day extension period of the first biologic initiation) to the occurrence of the safety event (which also occurred within the 90-day extension period for the first biologic). Tofacitinib treatment was discontinued when the safety event occurred, and there is a period of time where no treatment is used. For the second biologic initiation, one safety event occurred and exposure time is counted from Index date 3 to the safety event.

For the purpose of analysis, the patient has 2 biologic initiations and a tofacitinib initiation:

1st biologic initiation
|----------)---|---x--* (event occurring within 90 day extension period)
Index date 1

Tofacitinib initiation (occurring within 90-day extension period of 1st biologic)
|-----x) (event)
Index date 2

2nd biologic initiation
|----------x (event)
Index date 3

9.7.2. Primary analytic approach for malignancy and all-cause mortality events

As described in Section 9.3.4, for all malignancy events and all-cause mortality, the “once-exposed always at risk” approach will be used whereby the outcomes will be evaluated from drug initiation until the first event, loss to follow up or study end. If a patient switches to a new drug, the subsequent observation time will contribute to multiple therapies.

Note that for PML, both the 90-day risk window and the “once-exposed always at risk” approach will be applied.

While several studies have compared a “once-exposed always at risk” approach to a time on drug and other approaches and found similar rates of malignancy using an on-drug and ever

exposed approach[29,30,31,32], the primary analysis for this study will employ the "once-exposed always at risk" paradigm. Under this approach, follow-up for each cohort continues from the cohort index date until the first malignancy event, loss to follow-up, death or end of study. Follow-up for each exposure cohort will continue even after switching to a new drug in a different exposure cohort or discontinuation of treatment. This approach maximizes follow-up time and the ability to capture long latency events, i.e., events that occur or are detected months to years after exposure. Events will be double-counted if a patient indexed to a biologic switches to tofacitinib and a malignancy occurs subsequent to tofacitinib exposure. That is, the event will be assigned to both the biologic and the tofacitinib exposure cohorts as will the corresponding person-years since index to the respective cohorts. Tofacitinib is expected to be used in patients who have failed at least one other advanced systemic therapy. As such, switching is expected to be non-random with most tofacitinib patients having been included in the biologic cohort prior to initiation of tofacitinib. In such cases, the biologic rate will have more associated person-years and thus a relatively lower rate than the corresponding rate in the tofacitinib cohort.

Using this primary analytic approach, if neither tofacitinib nor biologics are associated with an increased risk of malignancy excluding NMSC, both exposure cohort rates will reflect the background rates of malignancy from the time of index to the end of the study period and a comparative effect measure will indicate no difference in rates. If tofacitinib is associated with an increased risk of malignancy excluding NMSC, a relatively higher rate will be observed in the tofacitinib-exposed cohort. The "once-exposed always at risk" approach is therefore able to detect an increased rate given the non-random switching expected to occur given use of biologics prior to tofacitinib and is consistent with previous studies evaluating the risk of individual biologics[29,30,31,32].

Additional analyses to evaluate potential confounders and the impact of different latency assumptions will be described in the SAP. Sensitivity analyses will be conducted that restrict the biologic cohort to patients who do not have any prior exposure to tofacitinib or other non-biologic advanced therapies and compare the characteristics of those biologic patients ever and never exposed to tofacitinib.

9.7.3. Sensitivity analyses

For all endpoints (both acute and non-acute), sensitivity analyses that censor follow-up time after a switch to a different treatment class (i.e., different exposure cohort) will also be conducted. Among patients indexed to a biologic cohort, follow-up will begin at index and continue until the first of a safety event of interest, switch to tofacitinib or immunomodulator/immunosuppressant, loss to follow-up, death, or study end date. Similarly, for tofacitinib, follow-up will begin at index and continue until the first of an event, switch to either a biologic or immunomodulator/immunosuppressant, loss to follow-up, death or study end date. While this approach eliminates the problem of double-counting, it may not allow for sufficient follow-up time for latent effects, thus reducing the statistical power to detect a higher risk of malignancy in tofacitinib-treated patients.

As an additional sensitivity analysis for acute events for which the primary analysis is the "as-treated approach" with a 90-day extension period applied after treatment discontinuation (as described above in Section 9.7.1), if a new medication is started during the 90-day

window after discontinuation of a previous medication, initiation of the new medication will stop the 90-day risk window, and any event prior to the new medication start will be assigned to the discontinued medication. As well for malignancy and all-cause mortality events, a 90-day risk window will be applied to the censoring at switch approach (i.e., if a malignancy or death occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy).

The schematic below provides hypothetical examples of patterns of event and treatment patterns to illustrate resulting contribution to rate calculation in the "once-exposed always at risk" and censoring at switch analytic models. For example, in the first row of the table below, the patient initiates a biologic, and remains on biologic treatment for 3 years, after which there is a switch to tofacitinib. Patient remains on tofacitinib for 2 years and experiences an event at during this time. Using the "once-exposed always at risk approach" which considers ever exposure vs. never exposure, follow-up for biologic treatment continues even after switching to tofacitinib so the biologic rate contribution is 1/5 (i.e., one event over a follow-up time of 5 years). Additionally, the event is also assigned to tofacitinib exposure as is the corresponding person-years since index (1/2). However for the censoring at switch approach, follow-up for the biologic is censored at switch to tofacitinb (biologic rate contribution is 0/3), and the event is attributed only to tofacitinib (1/2).

*: Biologic index date;
~: year on biologic;
^: tofacitinib index date;
-: year on tofacitinib;
O: discontinuation of systemic therapies such as biologics or immunomodulators/immunosuppressants;
=: year not on systemic therapy;
X: event.

	Once-Exposed Always at Risk		Censoring at Switch	
Treatment/Event pattern	Biologic rate contribution (events/person years)	Tofacitinib rate contribution (events/person years)	Biologic rate contribution (events/person years)	Tofacitinib rate contribution (events/person years)
* ~ ~ ~ ^ - - X	1/5	1/2	0/3	1/2
* ~ ~ ~ X	1/3	0/0	1/3	0/0
^ - - - O = = = X	0/0	1/6	0/0	1/6[a]
*~ ~ ~ ^ - - - ~ ~ ~ X	1/9	1/6	0/3	0/3
^ - - - - ~ ~ ~ X	0/0[b]	1/7	0/0[b]	0/4

a. Patients continue to be followed after index exposure discontinuation if they do not initiate another systemic therapy in a different class.
b. Patients are ineligible for biologic cohort index after tofacitinib index.
Note: if an event does not occur, person time will be allocated to rate denominator as described in table without corresponding event.

9.7.4. Subgroup analyses of primary and secondary safety events of interest

Several subgroup analyses will be performed for the primary and secondary safety events of interest. If, for a given subgroup, the sample size does not justify performing a comparative analysis (i.e., less than 80% power at the two-sided 0.05 significance level to detect a hazard ratio of 2.0), only descriptive analyses will be performed wherein the crude and age-adjusted rates will be presented along with 95% confidence intervals for the tofacitinib and comparative cohorts. In that case, no significance testing or additional modeling will be performed between the subgroups.

For both the primary and secondary safety events of interest, incidence rates for the tofacitinib cohort will be estimated overall and stratified by the following:

- Prior biologic use (prior biologic use vs. none; among those with prior biologic use, 1st biologic vs. 2nd biologic vs. ≥3 biologic)
- Patient age (patients aged ≥50 years vs. <50 years; patients aged ≥65 years vs. <65 years)
- Dose, i.e., ADD by time periods 1 (induction period) vs. 3 (purely maintenance period); time period 1 (induction period) vs. time period 2 (mixed induction/maintenance period)

For the outcome of malignancy excluding NMSC, incidence rates for the tofacitinib cohort will also be estimated overall and stratified by history of malignancy excluding NMSC.

For the outcome of VTE incidence rates for the tofacitinib cohort will be estimated overall and stratified by the following:

- Patients with ≥1 VTE risk factors vs. no VTE risk factors

For the outcomes of MACE and MI, incidence rates for the tofacitinib cohort will also be estimated overall and stratified by the following:

- Patients with ≥1 CV risk factors vs. no CV risk factors

For the outcome of lymphoma, incidence rates for the tofacitinib cohort will be estimated overall and reported for by the following lymphoma subtypes:

- Non-Hodgkin lymphoma (NHL)
- Hodgkin lymphoma
- Chronic lymphocytic leukemia (CLL)

Additionally, incidence rates for all safety events of interest in patients in the biologics cohort (Cohort 2) will be stratified by class of biologic [TNFi vs non-TNFi]), number of previous biologic treatments, and monotherapy vs. combination therapy.

If feasible, other stratified analyses such as the estimation of the incidence rates for VTE stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors will also be conducted (i.e., time period prior to 31 January 2020 vs. time period after 31 January 2020). Additionally, if feasible, stratification of the incidence rates for malignancy excluding NMSC, lung cancer, lymphoma, MACE and MI by time periods defined by changes in the SmPC for use in patients with malignancy and CV risk factors will be conducted (i.e. time period after June 2021).

9.7.5. Comparative analysis

The feasibility of conducting a comparative analysis will be evaluated at two interim time points (as discussed in Section 9.5), and at study end based on statistical power. However, as described in Section 9.5, the actual comparative analyses will only be performed at time of the final report if there are $\geqslant$500 patients in the tofacitinib cohort, which would allow for between 2.27 to 15.51 relative risk to be detected with 80% power at the 5% significance level, assuming 0% to 30% annual switching between tofacitinib and biologic cohorts.

Incidence rates of the safety events of interest will be compared between tofacitinib-treated UC patients (Cohort 1) and the comparator cohorts using propensity score matched multivariable Cox regressions adjusting for sex, age, year of treatment start, disease severity, comorbidities and other potential confounders. The Cox model will include a shared frailty term to account for the correlation between multiple observations from the same individual. The Cox model will also include any variables not in balance (standardized difference > 0.1) after propensity score adjustment. The proportional hazard assumption will be evaluated. The adjusted hazard ratio from the Cox model will be presented along with a 95% confidence interval.

All statistical analyses will be performed by KI using SAS version 9.4 (Cary, NC), STATA and R statistical software (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria). Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the 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.

9.7.6. Propensity Score Methods for Propensity Score Trimming and Matching

As discussed above, comparative analyses will be adjusted for differences in severity of disease and other confounders will be completed using propensity score matching methods. This will be conducted in two ways: matching and trimming. The steps for determining the propensity score trimmed populations will be as follows:

- Patient demographic and clinical factors at the time of index date, and prior treatment patterns will be compared between cohorts. Standardized differences and p-values generated from statistical tests comparing the tofacitinib cohort with the comparator cohorts will be generated.

- Standardized differences will inform the key covariates to be used to estimate a propensity score model (propensity for initiating tofacitinib vs. biologic therapy; propensity for initiating tofacitinib vs. immunomodulator/immunosuppressant, propensity for initiating tofacitinib vs. being treatment-naive). In addition to covariates with a standardized difference > 0.1, covariates potentially associated with the event of interest will be chosen a priori based on clinical expertise and input. These covariates may differ by the event being analyzed.

- The primary comparison will be in the full population of tofacitinib-treated patients and biologic-treated patients excluding only those drug initiations that fail to fall in the region of common support based on the estimated propensity score. This is sometimes called the propensity trimmed population (trimming patients with no similar propensity in each group). The use of the trimmed population provides a larger sample size for more precision and adjustment through multivariable modeling. The matched population will have a small sample size that minimizes bias with a trade-off of precision. If the sample allows, the primary analysis will use the trimmed population with a sensitivity analysis using the matched population. For the primary comparison, the sample of the patients from the comparator group matched to the full population of tofacitinib-treated patients will be created using propensity score matching with nearest neighbor algorithm without replacement allowing a maximum caliper width equal to 0.2 of the pooled standard deviation of the logit of the propensity score. Any patients that fail to match within this caliper width will be excluded.

9.7.7. Interim Reports

Interim reports will be descriptive, and will estimate the crude incidence rates (with corresponding 95% confidence intervals) of safety events of interest (including lymphoma subtypes for the lymphoma endpoint) by cohort. Additionally, in each interim report, the feasibility of conducting any confounding-controlled comparative analyses will be evaluated based on the observed tofacitinib sample size at the data cut-off date for that report.

9.7.8. Final Study Report

The final study report will include descriptive and, if there is sufficient tofacitinib sample size, detailed results of all comparative analyses and stratifications as outlined above.

There is some flexibility to include additional endpoints and stratification in the final report, and the report will contain populated tables in line with the shells to be documented in the SAP.

9.8. Quality control

This study uses data existing within SWIBREG. The data management of the SWIBREG register will include cleaning of data to remove illogical values, derive study variables, and structure the data in order to perform the required statistical analyses. All data management will be conducted on servers at Karolinska Institutet using standard statistical software including SAS, STATA, and R.

The quality control of data and statistical programs developed will include:

- Adherence to requirements and specifications outlined in the Statistical Analysis Plan (SAP). Any deviations will be reported.
- Review of joins between different data sources.
- Review of log files (errors, warnings, missing values, and notes).
- Review of distributions (histogram, min-max, median, percentiles, mean, standard deviation) of continuous variables and frequencies for all possible values of discrete variables.

9.9. Limitations of the research methods

This study is designed to monitor the safety of tofacitinib among UC patients within the clinical practice setting using data from SWIBREG, a well-established Swedish-based IBD register. SWIBREG has a national coverage of approximately 60%, and offers access to real-world data on IBD therapy. It allows for the long-term follow-up of IBD patients and their treatment outcomes via linkages with other national, well-established Swedish registers. Despite the strengths of this study, the possibilities of channeling bias and endpoint misclassification are of concern.

There are several limitations associated with the planned comparative analyses. Firstly, market uptake of tofacitinib will impact the size of the tofacitinib cohort, and cannot be determined a priori. As of 30 June 2020, there were approximately 2600 adult UC patients aged $\geqslant$18 years being treated with systemic agents such as biologics and other immunomodulators/immunosuppressants. Additionally, as this is a 6-year study, changes in the treatment landscape (e.g., approval of new medications for UC treatment) may further limit the size of the tofacitinib cohort. There is also a lack of a suitable comparator population for the tofacitinib cohort. As tofacitinib is a new UC medication, it is likely that patients treated with it will represent those with the most severe cases of disease, longer disease duration, history of multiple failed UC therapies and physical comorbidities that place patients at risk for events. Channeling may present as increased rates of safety events of interest. Incidence rates from the other UC cohorts may illuminate such channeling via stratification on key indicators of disease severity such as number of previous biologic treatments, patient characteristics and past therapies. Also, as per the EU SmPC, tofacitinib is to be prescribed to UC patients who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Thus, it is expected that the majority of patients receiving tofacitinib are likely to have cycled through multiple therapies, and may have previously failed at least one biologic UC therapy. Preliminary analysis of the Swedish registers indicate that as of 31 December 2019, the majority (approximately 64%) of UC patients prescribed tofacitinib had previously failed 3 or more systemic therapies (i.e., biologics and/or immunomodulators/immunosuppressants). As such, statistical power will also be limited by the ability to find “matchable” patients in the comparator cohorts. This increases the likelihood of residual confounding which could make results from a comparative analysis difficult to interpret. Residual confounding is also a limitation for the comparison of 5mg vs. 10mg BID maintenance regimens for tofacitinib since, as per the SmPC, for UC patients who are not at increased risk for VTE, the 10mg BID dose may be

considered only if the patient experiences a decrease in response on 5mg BID dose, and failed to respond to alternative treatment options for UC such as biologics. As such, patients on the 10mg BID maintenance dose are more likely to have disease that is harder to treat compared with patients on the 5mg BID maintenance dose.

Certain patient characteristics which may influence VTE outcomes (e.g., smoking status, obesity and immobilisation), cannot be reliably captured, and thus may limit data interpretation. Inherited coagulation disorders encompass a broad range of conditions, and only a limited number of these can be reliably captured in the Swedish registers. Previous VTE (i.e., history of VTE) can be reliably distinguished from new VTE if there is at least a 12 month period between events (in a recent unpublished, validation study [data on file], diagnostic VTE listings with shorter intervals than 12 months between them have turned out to be follow-up visits after the previous VTE episode, rather than a new VTE episode), i.e., if a patient with a history of VTE experiences a new VTE after initiating treatment with tofacitinib, if these VTE are less than 12 months apart, the second VTE listing would not be counted as a new VTE event). However, this is only applicable to the VTE outcome, and does not impact other safety outcomes for which a prior event may be considered in the patient medical history. Other VTE risk factors such as major surgery, MI within previous 3 months prior to index date, heart failure, diabetes, hypertension, malignancy and age are well captured in the Swedish registers. While immobilisation cannot be captured in the Swedish registers, including inpatient care due to UC (i.e., UC as main diagnostic listing) will capture hospitalized patients who will be immobilized, and who will also be at a potentially higher risk for VTE (consensus guidelines recommend thromboprophylaxis for all admitted patients with IBD in the absence of contraindications[21]). Additionally some CV risk factors such as smoking status (as previously mentioned) and baseline total cholesterol/HDL ratio cannot be adequately captured within the Swedish registers, and thus will limit the assessment of the MACE and MI endpoints.

For the outcome of lymphoma, the 3 main subtypes that can be adequately captured in the Swedish registers are NHL, Hodgkin lymphoma and CLL. Other lymphoma subtypes that do not fit into these 3 main categories will not be captured in the study and thus may limit the assessment of this outcome.

Event misclassification is of particular concern in a routine healthcare setting due to less stringent monitoring relative to clinical trials. Additionally, other factors such as errors in recording also need to be considered. While SWIBREG has an established system to identify and capture endpoint data, all events cannot be verified via source documentation (i.e., there is no adjudication of safety endpoints). However, linkages to other well-established, national healthcare registers with nearly complete coverage allow the register to obtain data on all safety events of interest (regardless of suspected causal relationship to the treatments).

Conclusions from this study may be limited to the duration of treatment captured, as well as the Swedish population. Generalizability to other populations, particularly those with different modes of healthcare delivery, may be limited.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

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

10.2. 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 is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., 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 scientific purpose, value and rigor follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology, and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), and the Karolinska's Institutet guidelines on Research Conduct.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Two interim summary reports will be generated. Analysis using linked register data through 5 years of follow up will be the basis for a final study report. The interim and final study reports will be submitted to regulatory authorities. Data may be used in regulatory communications external to Sweden for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for publication purposes and EMA will be notified upon acceptance for publication.

In the event of any prohibition or restriction imposed (e.g., 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.

13. REFERENCES

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14. VARIABLE DEFINITIONS

14.1. Appendix 1 – IBD Diagnosis and Outcome Definitions

Table 3. Relevant ICD codes for IBD determination

IBD type	ICD-7	ICD-8	ICD-9	ICD-10
	1964-1968	**1969-1986**	**1987-1996**	**1997-**
Ulcerative colitis (UC)	572,20 ; 572,21; 578,03	563,10 ; 563,99 ; 569,02	556	K51
Crohn's disease (CD)	572,00 ; 572,09	563,00	555	K50
Indeterminate colitis	-	-	-	K52.3

Table 4. Baseline Variables and Outcome Definitions

Outcome group	Outcome	ICD10/ATC	Data source	Comment	Validation
Baseline exposures to IBD drugs (12 months before index date)					The Swedish Prescribed Drug Register started on 1 July 2005 and contains complete data on the dispensation of all prescribed drugs in Sweden but very seldom drugs dispensed in hospital (e.g. infusions) or drugs bought over the counter (e.g. paracetamol). In a not yet published validation study of >2300 treatment episodes with biologics in Swedish IBD patients (personal communication dr Bröms [postdoc in dr Olén's group]), the sensitivity for biological IBD treatments in the Prescribed drug register and the National Patient Register combined were 80%. Of all individual drugs, the sensitivity was high for adalimumab, golimumab, and ustekinumab (89%, 90%, and 88%, respectively). For infliximab, 41% of treatment episodes in the medical charts were ever captured by records in Prescribed Drug Register and the National Patient Register (PDR/NPR) and only 19% of vedolizumab treatment episodes were captured. The Swedish IBD quality register has an ever increasing coverage and is increasingly used as a decision tool in clinical practice. For patients registered in SWIBREG, the sensitivity for biologics can be assumed to be very high, especially in combination with the Prescribed Drug Register and the National Patient Register[15,33],.
Oral corticoid steroid use			Prescribed Drug Register	Filled prescriptions only	
	Betamethasone	H02AB01			
	Dexamethasone	H02AB02			
	Methylprednisolone	H02AB04			
	Prednisolone	H02AB06			
	Prednisone	H02AB07			
	Hydrocortisone	H02AB09			
	Cortisone	H02AB10			
Immunomodulators / Immunosuppressants			Prescribed Drug Register	Filled prescriptions only	

	Azathioprine	L04AX0 1			
	Mercaptopurine	L01BB02			
	Methotrexate	L04AX03/L01BA01			
	Tacrolimus	L04AD02			
	Cyclosporin	L04AD01			
	Azathioprine	L04AX0 1			
Biologic			Prescribed Drug Register or National Patient register or SWIBREG	Filled prescriptions, or records of infusions/injections, or records in SWIBREG	
	Infliximab	L04AB02 (L04AA12 before 2008)			
	Adalimumab	L04AB04 (L04AA17 before 2008)			
	Golimumab	L04AB06			
	Vedolizumab	L04AA33			
Exposure to some non IBD medication (12 months before index date)					
	Antimicrobials	J01, J02, J04, J05			
	Anticoagulant	B01AA, B01AB, B01AC, B01AE, B01AF, B01AX			
	Beta blocker	C07A, C07F			
	Bisphosphonates	B05BA, B05BB			
	Narcotics	N07BC, N02A, N01AH			
	Oral NSAID (Non-cox)	M01AB01, M01AB05, M01AB55, M01AB15, M01AC01, M01AC02, M01AC05, M01AC06, M01AE01, M01AE51, M01AE02, M01AE03 M01AE09, M01AE14, M01AE17, M01AX01			
	Oral NSAID (Cox)	M01AH01, M01AH04, M01AH05			
	PPI drug	A02BC			
	Statins	C10AA			
Comorbidities at baseline (i.e. within 12 months of index date)					Please see below (“serious infections” and “AMI”).
	Stroke	I60-I64			
	Ischemic heart disease	I20-I25			
	Hypertension	I10-I15			
	Diabetes mellitus	E10-E14, O24			
	Heart failure	I50			
	Non-alcoholic fatty liver disease	K76.0			

Hereditary coagulation disorders					
	Primary and other thrombophilia	D68.5 D68.6			
	Venous Thromboembolism in adults to patients	ICD-codes as specified below.	Parents identified through linkage to the multigeneration register		
Serious infections			Patient Register, inpatient diagnoses only	Main or secondary diagnosis, inpatient diagnosis only Note, this will **not** include parenteral antibiotics given in an outpatient setting, which is extremely rare in Sweden.	The algorithms to detect serious infections, opportunistic infections, and Herpes Zoster reactivation in the Patient Register has not been specifically validated in patients included in SWIBREG, but the Patient Register itself is subject to strict quality assurance routines and has been validated several times[18].
	Infectious diseases, by type of infectious agent	A00-B99			
	Spleen abscess	D73.3			
	Thyroid abscess	E06.0			
	Thymus abscess	E32.1			
	Meningitis	G00-G02, G04.2			
	Encephalitis, CNS abscess	G05-G07			
	Eyelid abscess	H00.0			
	Purulent eye infection	H44.0			
	Infectious external otitis	H60.0-H60.3			
	Otitis media	H66-H67			
	Mastoiditis	H70			
	Infectious pericarditis	I30.1			
	Infectious myocarditis	I40.0			
	Acute infections in upper and lower airways	J00-J22			
	Chronic sinusitis	J32			
	Nose abscess	J34.0			
	Peritonsillitis	J36			
	Vocal cord abscess	J38.3			
	Pharyngeal abscess	J39.0-J39.1			
	Chronic obstructive lung disease with acute lower airway infection	J44.0			
	Lung abscess	J85			
	Pleura empyema	J86			
	Tooth infections	K04.4, K04.6, K04.7			
	Osteitis in the jaw	K10.2			

Salivary gland abscess	K11.3
Mouth abscess	K12.2
Tongue abscess	K14.0
Small or large bowel diverticulitis with perforation or abscess	K57.0, K57.2, K57.4, K57.8
Perianal abscess	K61
Bowel abscess	K63.0
Peritonitis	K65.0, K65.1, K65.2, K65.9
Skin infections	L00-L08
Infectious dermatitis	L30.3
Infectious arthritis	M00-M01
Vertebral infections	M46.2-M46.5
Infectious myositis	M60.0
Infection in tendon sheath	M65.0
Infectious bursitis	M71.0, M71.1
Necrotising fasceitis	M72.6
Osteomyelitis	M86
Acute infectious glomerulonephritis	N10
Chronic infectious glomerulonephritis	N11
Infectious glomerulonephritis	N12
Pyonephrosis	N13.6
Renal abscess	N15.1
Kidney infection	N15.9
Cystitis	N30.0, N30.8
Urethra abscess	N34.0
Prostate abscess	N41.2
Hydrocele infection	N43.1
Orchitis et epididymitis	N45
Penile abscess	N48.2
Breast abscess	N61
Salpingitis et oophoritis	N70
Infections in the female pelvic organs	N73
Abscess in the Bartholini gland	N75.1

Opportunistic infections excluding Herpes Zoster			Patient register, inpatient diagnoses only	Main or secondary diagnosis. Note, this will **not** include parenteral antibiotics given in an outpatient setting, which is extremely rare in Sweden.	As above
	Salmonella infections	A02			
	Tuberculosis in airways, verified histologically or microbiologically	A15			
	Tuberculosis in airways, *unverified* histologically or microbiologically	A16			
	Tuberculosis in the nervous system	A17			
	Tuberculosis in other organs	A18			
	Tuberculosis miliaris	A19			
	Mycobacterial infections	A31			
	Listeriosis	A32			
	Nocardiosis	A43			
	Legionnaire disease	A48.1			
	Coccidioidomycosis	B38			
	Histoplasmosis	B39			
	Blastomycosis	B40			
	Aspergillosis	B44			
	Cryptococcosis	B45			
	Toxoplasmosis	B58			
	Pneumocystosis	B59			
Herpes Zoster			Patient register, inpatient component.	Main or secondary diagnosis	As above
		B02			
Malignancy			The Cancer register		About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%[17].
		All non-benign tumors, except C44 and D04 (ICD7=191), and basal cell cancers			

Lung cancer		ICD-7: 162.1	The Cancer Register		
Lymphoma	All non-Hodgkin Lymphoma All Hodgkin Lymphoma Chronic lymphocytic leukemia	ICD-7: 200, 202 ICD-7: 201 ICD-7: 204.1	The Cancer Register		About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%[17].
Acute Myocardial Infarction (AMI)			Patient register, in- or outpatient component. Or in Cause of Death register	Main or secondary diagnosis	See "Serious infections" above for general validations of the Patient Register. The definition of Major Adverse Cardiovascular Events (MACE) has previously been validated in a Swedish early Rheumatoid Arthritis cohort, with a positive predictive value of 95%. In addition, a regional validation study of hospitalized AMI and stroke found positive predictive values of 96% and 94% respectively, in the period 1977 to 1987[22].
	Instable angina pectoris Acute myocardial infarction	I20.0 I21			
Stroke			Patient register, in- or outpatient component. Or in Cause of Death register	Main or secondary diagnosis	See AMI above
	Cerebral bleeding or infarction	I60 – I64			
Cardiovascular death			Cause of death register	Underlying cause of death	See AMI above
		Any from the I chapter			
Major Adverse Cardiovascular Event (MACE)			Patient register, in- or outpatient component. Or in Cause of Death register	Main or secondary diagnosis	See AMI above
	Cardiovascular death (**death** due to MI, sudden cardiac **death**, **death** due to heart failure, **death** due to stroke, **death** due to CV procedure, **death** due to	.			

	CV hemorrhage, **death** due to other CV causes [e.g. peripheral artery disease]); non-fatal MI, non-fatal stroke (see codes above)				
Venous thromboembolism (deep venous thrombosis [DVT] and pulmonary embolism [PE])			Patient register, in- or outpatient component.	Main or secondary diagnosis	In a nationwide cohort of pregnant women, the majority of first VTEs recorded in the Swedish inpatient data (91%) were accompanied by anticoagulant therapy following the event, whereas among patients with a first VTE recorded in the outpatient setting only a minority were (43%)[34].
	Pulmonary embolus	I26			
	Thrombosis venae portae	I81			
	Other venous emboli and thrombosis	I82		Incl Budd-Chiari syndrome, Thrombophlebitis migrans, vena cava thrombosis, vena renalis thrombosis, thrombosis in other veins including vena hepatica	
	Venous thrombosis in cerebral veins (that did not lead to infarction), intraspinal veins, mesenteric vein	I63.6, I67.6, G95.1, K55.0			
	Embolus or thrombosis after abortion, extrauterine pregnancy, or molar pregnancy	O08.2, O08.7			
	Cerebral vein thrombosis, or thrombosis NOD	O22.5, O22.9			
	Deep vein thrombosis during postpartum period, cerebral vein thrombosis, or thrombosis NOD	O87.1, O87.3, O87.9			
	Thrombosis or embolus after infusion,	T80.1			

	transfusion, or injection (as treatment)				
PML (progressive multifocal leucoencephalopathy)			**Inpatient component of Patient Register.**	**Main diagnosis**	**See Serious Infections above**
		A81.2			
Death (all-cause mortality)			**Cause of death register**	**Underlying cause of death**	There is an overall 77% agreement between the cause of death from death certificates (on which data in the cause of death register is based) and the cause of death expected based on case summaries. Agreement is higher in younger age groups (98% and 91% agreement in age groups 0–44 years and 45–64 years, respectively) and for some diagnostic groups. For example, there is higher agreement among deceased with malignant neoplasms as the underlying cause of death (Overall, 86% concordance between medical records and the cause of death register was reported for prostate cancer (increasing to 96% in those who died younger than 60 years old), and a similar level of agreement has been reported for cardiovascular disease deaths at a high level of classification (ICD-10 codes at the three digit level)[16].
		Any cause if death			
Gastrointestinal perforations					Please see “infections” above.
	Perforation of esophagus Acute gastric ulcer with perforation Acute gastric ulcer with both hemorrhage and perforation K25.5 Chronic or unspecified gastric ulcer with perforation K25.6 Chronic or unspecified gastric ulcer with both hemorrhage and perforation K26.1 Acute duodenal ulcer with perforation K26.2 Acute duodenal ulcer with both hemorrhage and perforation	K22.3 K25.1 K25.2 K25.5 K25.6 K26.1 K26.2 K26.5 K26.6 K27.1 K27.2 K27.5 K27.6 K28.1 K28.4 K28.5 K28.6 K31.6 K35.1			

K26.5 Chronic or unspecified duodenal ulcer with perforation	K35.0 K51.513 K51.514
K26.6 Chronic or unspecified duodenal ulcer with both hemorrhage and perforation	K57.0 K57.00 K57.01 K57.2
K27.1 Acute peptic ulcer, site unspecified, with perforation	K57.20 K57.21 K57.4
K27.2 Acute peptic ulcer, site unspecified, with both hemorrhage and perforation	K57.40 K57.41 K57.8
K27.5 Chronic or unspecified peptic ulcer, site unspecified, with perforation	K57.80 K57.81 K60.3
K27.6 Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and perforation	K60.4 K60.5 K61.1 K61.2
K28.1 Acute gastrojejunal ulcer with perforation	K61.3 K63.0
K28.2 Acute gastrojejunal ulcer with both hemorrhage and perforation	K63.1 K63.2 K65
K28.4 Chronic or unspecified gastrojejunal ulcer with hemorrhage	K65.0 K65.1 K65.2 K65.3
K28.5 Chronic or unspecified gastrojejunal ulcer with perforation	K65.8 K65.9 K68.1
K28.6 Chronic or unspecified gastrojejunal ulcer with both hemorrhage and Perforation	K68.11 K68.12 K68.19 N32.1
K31.6 Fistula of stomach and duodenum	

K35.1 Perforated appendicitis with abscess
K35.0 Acute appendicitis with perforation
K51.513 Left sided colitis with fistula
K51.514 Left sided colitis with abscess

K57.0 Diverticulitis of small intestine with perforation and abscess
K57.00 Diverticulitis of small intestine with perforation and abscess without bleeding
K57.01 Diverticulitis of small intestine with perforation and abscess with bleeding
K57.2 Diverticulitis of large intestine with perforation and abscess
K57.20 Diverticulitis of large intestine with perforation and abscess without bleeding
K57.21 Diverticulitis of large intestine with perforation and abscess with bleeding
K57.4 Diverticulitis of both small and large intestine with perforation and abscess
K57.40 Diverticulitis of both small and large intestine with perforation and abscess without bleeding
K57.41 Diverticulitis of both small and large intestine with perforation and abscess with bleeding

K57.8 Diverticulitis of intestine, part unspecified, with perforation and abscess
K57.80 Diverticulitis of intestine, part unspecified, with perforation and abscess without bleeding
K57.81 Diverticulitis of intestine, part unspecified, with perforation and abscess with Bleeding

K60.3 Anal fistula
K60.4 Rectal fistula
K60.5 Anorectal fistula

K61.1 Rectal abscess
K61.2 Anorectal abscess
K61.3 Ischiorectal abscess
K63.0 Abscess of intestine

K63.1 Perforation of intestine (nontraumatic)
K63.2 Fistula of intestine

K65 Peritonitis
K65.0 Generalized (acute) peritonitis
K65.1 Peritoneal abscess
K65.2 Spontaneous bacterial peritonitis
K65.3 Choleperitonitis

K65.8 Other peritonitis
K65.9 Peritonitis, unspecified
K68.1 Retroperitoneal abscess

	K68.11 Postprocedural retroperitoneal abscess K68.12 Psoas muscle abscess K68.19 Other retroperitoneal abscess N32.1 Vesicointestinal fistula				
Fractures	Skull/face Neck Ribs/chest Lumbar spine/pelvis Shoulder/humerus Forearm Wrist/hand Femur Ankle/wrist Foot Fractures on multiple body parts, Location of fracture not defined in detail	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08 T10 T12 T14.2	Patient register, in- or outpatient component.	Main or secondary diagnosis	The PPV for fractures in the Swedish NPR is extremely high: a validation of 647 patient charts the PPV of fracture in Swedish patient records was 1.00[37]. There is high accuracy for both a diagnosis of hip fracture and a fracture of any type in the Swedish Patient Register[37,38].

15. LIST OF TABLES

16. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance, Post-Authorisation Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG)

EU PAS Register® number: **Study reference number (if applicable): A3921344**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 & 8
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8 & 9.2.1 & 9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.1

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8 & 9.7
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6 & 9.1
4.2.2 Age and sex	☒	☐	☐	9.2.1 & 9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	8, 9.2.1 & 9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.3.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1 & 9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.1, 9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.2.1, 9.3.2.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	

Comments:

Details related to dosing to be provided in a statistical analysis plan (SAP). Due to significant differences in underlying disease severity between tofacitinib-treated patients and comparator cohorts, there are several anticipated challenges with the planned comparative analyses.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.6 & 14.1
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.6, 14.1
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	14.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.1

Comments:

Details to be provided in a statistical analysis plan (SAP).

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Details to be provided in statistical analysis plan (SAP).

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5, 9.7.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3 & 10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1 & 10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Nana Koram

Date: 09/02/2022

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

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