Study information

Title	A Long-Term, Observational Study within the Corrona Inflammatory Bowel Disease (IBD) Registry to Characterize the Safety of Tofacitinib in Patients with Ulcerative Colitis in the Post-Approval Setting
Protocol number	A3921329
Protocol version identifier	3.0
Date	24 January 2020
EU Post Authorization Study (PAS) register number	EUPAS30314
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	The overall goal of the study is to characterize the safety of tofacitinib (all approved formulations, including the immediate-release formulation [5mg and 10mg twice daily] and the extended-release formulation [11mg and 22mg once daily]) in ulcerative colitis (UC) patients in the post-approval setting. 1. The primary objective is to assess the incidence of malignancy, excluding non-melanoma skin cancer (NMSC), in adult UC patients exposed to tofacitinib in the course of routine clinical care compared to other medications approved to treat UC. 2. The secondary objectives are to assess the incidence of NMSC, opportunistic infections (e.g. tuberculosis, opportunistic mycoses), major adverse cardiac events

	(MACE), venous thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), hepatic events, serious infections, herpes zoster (HZ) reactivation, progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, surgery for UC and all-cause mortality in adult UC patients exposed to tofacitinib in the course of routine clinical care compared to other medications approved to treat UC.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	Adverse Event
AEM	Adverse Event Monitoring
AZA	Azathioprine
CA	California
CBC	Complete blood count
CEO	Chief Executive Officer
CI	Confidence Interval
CRF	Case Report Form
CSO	Chief Statistical Officer
CT	Connecticut
CV	Cardiovascular
DVT	Deep venous thrombosis
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FL	Florida
g	Gram
GA	Georgia
GI	Gastrointestinal
HBV	Hepatitis B Virus

Abbreviation	Definition
Hg	Mercury
HR	Hazard ratio
HZ	Herpes zoster
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
IEC	International Ethics Committee
IL	Interleukin
IP	Internet Protocol
IRB	Institutional Review Board
IS	Information Service
IT	Information Technology
JAK	Janus Kinase
kg	Kilogram
KS	Kansas
LA	Louisiana
MA	Massachusetts
MACE	Major adverse cardiac event
MD	Maryland
MI	Michigan
mg	Milligram
mm	Millimeter
MS	Missouri

Abbreviation	Definition
NBSM	Non-biologic systemic (immunosuppressant) medication
NC	North Carolina
NIS	Non-interventional study
NMSC	Non-melanoma skin cancer
NV	Nevada
NY	New York
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PE	Pulmonary embolism
PML	Progressive multifocal leukoencephalopathy
PRO	Patient-reported Outcome
PROMIS®	Patient-Reported Outcomes Measurement Information System
RA	Rheumatoid Arthritis
RI	Rhode Island
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	South Carolina
SCCAI	Simple Clinical Colitis Activity Index
SIAC	Site Investigator Advisory Committee
SIE	Serious Infection Event
SOP	Standardized Operating Procedure

Abbreviation	Definition
TBD	To Be Determined
TAE	Targeted Adverse Event
TN	Tennessee
TNF	Tumor Necrosis Factor
TX	Texas
TyK2	Tyrosine Kinase 2
UC	Ulcerative Colitis
URL	Universal Resource Locator
US	United States
VA	Virginia
WPAI	Work Productivity and Activity Impairment
XR	Extended-release

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

- Title: A Long-Term, Observational Study within the Corrona Inflammatory Bowel Disease (IBD) Registry to Characterize the Safety of Tofacitinib in Patients with Ulcerative Colitis in the Post-Approval Setting

- Name and affiliation of main author (s)
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  Pfizer, Inc.

  On behalf of the Corrona team:

  Carol J. Etzel, PhD
  Corrona, LLC

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  Corrona, LLC

- Rationale and background: Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases that was approved in the United States (US) in May 2018 for use in patients with moderate-to-severe ulcerative colitis (UC). Malignancy has been identified as a potential risk in the tofacitinib risk management plan (RMP). Thus to enable the long-term assessment of rare adverse events and safety endpoints with long latency periods such as malignancy, a post-approval, population-based study of tofacitinib-exposed patients will be conducted using data collected as part of the Corrona Inflammatory Bowel Disease (IBD) Registry in a prospective manner.

  In this protocol, except where otherwise specified (e.g. specific dose-related analyses), all references to tofacitinib are intended to include tofacitinib immediate-release (Xeljanz) and tofacitinib extended-release (Xeljanz XR) formulations.

- Research question and objectives: The overall goal of the study is to characterize the safety of tofacitinib (including both the immediate-release [5mg and 10mg twice daily] and the extended-release [11mg and 22mg once daily] formulations) in UC patients in the post-approval setting.

  1. The primary objective is to assess the incidence of malignancy, excluding non-melanoma skin cancer (NMSC), in adult UC patients exposed to tofacitinib in the course of routine clinical care compared to other medications approved to treat UC.
  2. The secondary objectives are to assess the incidence of the following events (includes events specified by the US Food and Drug Administration (FDA), as well as events identified as potential risks in the tofacitinib RMP): NMSC, opportunistic infections (e.g. tuberculosis, opportunistic mycoses), major adverse cardiac events (MACE), venous thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), hepatic events (serious or requiring liver biopsy), serious infections, herpes zoster (HZ) reactivation, progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, surgery for UC and all-cause mortality in adult UC

patients exposed to tofacitinib in the course of routine clinical care compared to other medications approved to treat UC.

- Study design: This is a population-based, observational cohort study of tofacitinib-exposed UC patients using data collected prospectively as part of the Corrona IBD Registry. Corrona captures patient enrollment and follow-up data as part of routine clinical care. All patients receive standard care treatments prescribed by their treating gastroenterologist (also referred to as "investigator"), in accordance with the FDA-approved drug labeling, and all treatment decisions are the sole responsibility of the investigator and not dictated by the study protocol.

- Population: The study population will comprise all patients who receive tofacitinib within the Corrona IBD registry, following US approval and marketing, through the end of the study period (estimated to be 8 years from the study launch date). Two comparator populations will be assembled consisting of patients with UC, irrespective of line of therapy, who are not receiving tofacitinib. The Corrona IBD Registry is an existing, prospective, multicenter, observational registry for adult patients with IBD (including UC), although only patients diagnosed with UC will be included in this post-authorization safety study.

    - The primary comparator group for the tofacitinib-exposed group will consist of UC patients exposed to an anti-tumor necrosis factor (TNF) biologic medication approved for treatment of UC (i.e. adalimumab, golimumab (Simponi subcutaneous formulation), or infliximab).

    - The secondary comparator group will consist of UC patients exposed only to non-biologic immunosuppressant therapies approved for the treatment of UC (e.g., immunosuppressants such as 6-mercaptopurine (6-MP), azathioprine (AZA), tacrolimus, cyclosporine or sulfasalazine), i.e. patients must be naïve to biologic and JAK therapy.

      Note: Other biologics (including, but not limited tovedolizumab and ustekinumab) approved for UC may be examined descriptively as a potential analysis in the Final Report, if sufficient data should accumulate during the study period.

- Variables: Baseline demographic (e.g. age, gender, race/ethnicity) and clinical variables will be reported. The study will evaluate a range of safety outcomes associated with therapies approved for the treatment of UC, including malignancies (excluding NMSC), NMSC, opportunistic infections, MACE, venous thromboembolic events (DVT and PE), hepatic events, serious infections, herpes zoster (HZ) reactivation, progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, surgery for UC and all-cause mortality.

- Data sources: This study will use data collected as part of the Corrona IBD Registry. Patients are enrolled in the registry during regularly-scheduled office visits. Upon enrollment, physicians complete a Provider Enrollment Questionnaire that includes a Simple Clinical Colitis Activity Index (SCCAI), pouchitis history and a Mayo Score (partial). Patients also complete an Enrollment Questionnaire that includes questions

about Healthcare Utilization, the Patient-Reported Outcomes Measurement Information System (PROMIS®) and the Work Productivity and Activity Impairment questionnaire (WPAI).

After the enrollment visit, patients and providers then complete Corrona IBD Registry Follow-up Questionnaires during regularly scheduled clinical encounters approximately every 6 months.

In the event of a patient death, withdrawal from the study, or loss to follow-up, the Patient Exit Questionnaire is completed by the provider.

Adverse events which occur during participation in the registry are reported on Targeted Adverse Event (TAE) Questionnaires. All serious adverse events (SAEs) are reportable on a TAE Questionnaire for the purposes of the registry.

- Study size: An estimated sample size of 1,143 tofacitinib-treated patients (with 5,715 total comparator patients; 1:5 tofacitinib:comparator anti-TNF ratio) will be accrued over a 5-year period. Follow-up will continue for three years after the last patient has accrued (for a total study duration of 8 years). The study is designed to detect an increased risk of malignancy (hazard ratio of 1.8 or greater) in the tofacitinib cohort with 90% power at the two-sided 0.05 significance level. Sample size estimations were calculated using PASS 16.0.3.

- Data analysis: For the safety endpoints of interest, descriptive statistics, counts and proportions, unadjusted cumulative incidence proportions, and unadjusted incidence rates (i.e., number of events per person-years) and associated two-sided 95% confidence intervals will be calculated as appropriate and compared between groups. Depending on data availability, subgroup analyses (disease severity, tofacitinib dose, prior treatment group (mechanism of action) and/or comorbidity status) may be performed.

  The primary summary of reporting rates of events will be based on survival analysis of time to first event based on an index date defined for each population (for tofacitinib initiators this will be date of initiation) with appropriate censoring rules applied (based on therapy switches, last follow-up visit, end of study) for those who do not experience an event by end of follow-up period. Rates will be expressed as events/100 person-years of follow-up. A Cox regression model will be estimated to analyze time to first event for each safety event of interest and compare rates of events between the tofacitinib study population and the two defined comparator groups (biologics and immunosuppressant groups).

- Milestones:

  a. Start of data collection: 30 June 2019
  b. End of data collection: 30 June 2027
  c. Interim report: 30 June 2024
  d. Final study report: 31 December 2027

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1	May 2019	Study Information	Version, title updated	[redacted]
		3. Responsible Parties	Pfizer contact details updated	
		4. Abstract	Title, population, study size updated	
		6. Milestones	Timing updated to reflect new study duration	
		7. Rationale and Background	Removed disease severity and dosing qualifiers (population)	
		8. Research Question and Objectives	Removed disease severity and dosing qualifiers (population)	
		9.2.1 Inclusion Criteria	Removed disease severity qualifier; NBSM recruitment	
		9.3.1 Study Outcomes	Clarifying text added, primary comparative analysis	
		9.3.1.4 Opportunistic Infection	Case definition reference (Winthrop) added; clarifying text regarding pathogen capture	
		9.3.1.5 Herpes Zoster	Supplemental text added for consistency	
		9.3.2 Corrona IBD Registry Safety Endpoint Procedures	Clarifying text added	
		9.3.3.1 Drug Exposure and Cohort Identification for Malignancy Outcomes	Clarifying text added	
		9.3.3.2 Drug Exposure and Cohort Identification for Non-malignancy Outcomes	Clarifying text added	
		9.3.4.1 Switching	Clarifying text added	
		9.3.4.1.2 Switching Between Medication Cohorts	Clarifying text added	
		9.5 Study Size	Revised to incorporate FDA feedback; clarifying text added	
		9.7 Data Analysis	Clarifying text added	
		9.7.1 Patient Demographic and Clinical Characteristics	Variables added to incorporate FDA feedback	
		9.7.2 Analysis of Primary Objective of Malignancy Incidence	Updated to include modeling details of semiparametric shared frailty model	
		9.7.3 Analysis of the Secondary Objective of NMSC and Non-malignancy Incidence	Updated to include modeling details of semiparametric shared frailty model	
		9.7.4 Subgroup Analysis of Primary and Secondary Outcomes	Clarifying text added	
		9.7.5 Propensity Score Methods for PS Trimming and Matching	Clarifying text added	
		9.7.6 Analyses for Interim, Comparative Safety Report	Clarifying details added to address timing and approach to interim report	
Amendment 2	January 2020	Study Information	Updated version, title, and EU Post-authorization study register number	[redacted]
		2. List of Abbreviations	Updated to include extended-release (XR)	

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		4. Abstract: rationale and backgtround	Updated study scope to include extended-release (XR) formulation, approved doses	
		6. Milestones	Updated with date of EU PAS registration	
		7. Rationale and Background	Updated study scope to include extended-release (XR) formulation, approved doses	
		8. Research Question and Objectives	Expanded list of Other Biologic examples to include ustekinumab	
		8.2 Secondary Objectives	Clarifying edits made to the following endpoints: Thromboembolism changed to Venous Thromboembolism (VTE); Herpes Zoster (HZ) changed to Herpes Zoster (HZ) reactivation; Death changed to All-cause mortality	
		9.3.1.5 Herpes Zoster	Section title, endpoint revised to Herpes Zoster *Reactivation*	
		9.3.1.6 Thromboembolism	Section title, endpoint revised to *Venous* Thromboembolism	
		9.3.1.11 Death	Section title, endpoint revised to All-cause Mortality	
		9.3.3. Drug Exposure	Updated to clarify number of patients expected to be treated with tofacitinib for ⩾ 18 months	
		9.7.1. Patient Demographics and Clinical Characteristics	Updated to specify approved extended-release doses, for dosing-related analyses	
		9.7.4. Subgroup Analyses of Primary and Secondary Outcomes	Updated text to include subgroups based on patient age, including patients <65 years of age vs. ≥65 years	
		9.7.5 Propensity Score Methods for Propensity Score Trimming and Matching	Added clarifying text to biologic initiators reference to specify *anti-TNF* biologic initiators	
		12. Plans for Disseminating and Communicating Study Results	Updated text to specify within 1 business day as timeframe for reporting of any urgent safety measures	

6. MILESTONES

Milestone	Planned date
Start of data collection	30 June 2019
End of data collection	30 June 2027
Interim report	30 June 2024
Registration in the EU PAS register	28 June 2019
Final study report	31 December 2027

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. UC presents significant health and socioeconomic burdens for the individual patient and society[2]. In North America, incidence rates range from 2.2 to 19.2 cases per 100,000 person-years[3,4]. In one of the largest studies based upon nine million health insurance claims, the prevalence of UC in adults in the United States (US) was 238 per 100,000 population[5].

Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the US in May 2018 for the treatment of adults with moderate-to-severe UC (use in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine (AZA) and cyclosporine is not recommended). Two formulations of tofacitinib have been approved in the US: the Xeljanz immediate release formulation at a dose of 5mg twice daily and 10mg twice daily, and the Xeljanz extended-release (XR) formulation at a dose of 11mg once daily and 22mg once daily.. Malignancy is a potential risk with the use of tofacitinib. Spontaneous reporting alone will not be sufficient to adequately assess this potential risk associated with the long-term use of tofacitinib in this patient population. Thus this long-term, observational study in the US is designed to evaluate the long-term safety of tofacitinib versus other approved therapies used in the treatment of adults with UC. In this protocol, except where otherwise specified (e.g. specific dose-related analyses), all references to tofacitinib are intended to include tofacitinib immediate-release (Xeljanz) and tofacitinib extended-release (Xeljanz XR) formulations.

The Corrona IBD registry will be the data source for this study. The registry is equipped to evaluate safety endpoints immediately post-launch of tofacitinib, as well as over an extended period of time (i.e., 8 years). The Corrona IBD database will be queried to identify UC patients treated with tofacitinib and capture the occurrence of safety endpoints of interest [primary endpoint is malignancy, excluding non-melanoma skin cancer (NMSC) and

secondary endpoints of interest include NMSC, opportunistic infections, major adverse cardiac events (MACE), thromboembolic events, serious infection events (SIEs), herpes zoster (HZ), progressive multifocal leukoencephalopathy, (PML), hepatic adverse events, gastrointestinal (GI) perforations, surgery for UC, and death] relative to patients treated with biologic and non-biologic immunosuppressant medication (excluding 5-aminosalicylic acid [5-ASA] and corticosteroid therapies) approved for UC.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing requirement to the US Food and Drug Administration (FDA).

8. RESEARCH QUESTION AND OBJECTIVES

The goal of the study is to characterize the safety of tofacitinib (all approved formulations, including the immediate-release [5mg and 10mg twice daily] and extended-release [11mg and 22mg once daily] formulations) in UC patients in the post-approval setting. The overall research questions is: “What are the long-term effects of tofacitinib vs. other approved UC therapies in adult patients with UC?”.

Comparator populations will include two separate populations:

- The primary comparator group for the tofacitinib-exposed group will consist of patients exposed to an anti-TNF biologic medication approved for treatment of UC (i.e. adalimumab, golimumab (Simponi subcutaneous formulation), or infliximab).
- The secondary comparator group will consist of patients that are naïve to biologic and JAK therapy but exposed only to non-biologic immunosuppressant therapies for treatment of UC (e.g., immunosuppressants such as 6-MP, azathioprine, tacrolimus, cyclosporine or sulfasalazine).

  Note: Other biologics (including, but not limited to vedolizumab and ustekinumab) approved for UC may be examined descriptively as a potential analysis in the Final Report, if sufficient data should accumulate during the study period.

8.1 Primary objective

The primary objective of the study is to assess the incidence of malignancy, excluding NMSC, in adult UC patients exposed to tofacitinib in the course of routine clinical care compared to other medications approved to treat UC.

8.2 Secondary objectives

The secondary objectives of the study are to assess the incidence of NMSC, opportunistic infections (e.g. tuberculosis, opportunistic mycoses), SIEs, MACE, HZ reactivation, PML, venous thromboembolic events: (DVT) and pulmonary embolism (PE), hepatic events, GI perforations, surgery for UC, and all-cause mortality in adult UC patients exposed to tofacitinib in the course of routine clinical care compared to comparator medications approved to treat UC.

9. RESEARCH METHODS

9.1. Study design

This is a population-based, observational cohort study of tofacitinib-exposed UC patients using data collected as part of the Corrona IBD Registry in a prospective manner. Corrona captures patient enrollment and follow-up data as part of routine medical practice. All patients receive standard of care treatments prescribed by their treating gastroenterologist (also referred to as "investigator"), in accordance with the FDA-approved drug labeling, and all treatment decisions are the sole responsibility of the investigator and not mandated by study protocols.

Enrollment in the Corrona IBD Registry is voluntary and eligibility is based on use of a medication (biologic or non-biologic systemic immunosuppressant) that has been approved for use in UC at the time of enrollment. Duration of therapy and subsequent therapies, if any, are not mandated by Corrona guidelines or by this protocol.

Enrollment for this study is estimated to take approximately 5 years, and follow-up will continue for a minimum of 3 years from the time of enrollment of the last patient (last patient first visit), with total study duration of 8 years. Should market uptake be slower than anticipated, an extension of the enrollment period may be considered to ensure sufficient power for primary outcome analyses.

9.2. Setting

The Corrona IBD Registry is an existing, prospective, multicenter, observational registry for adult patients with IBD (including UC). The population to be included in this study will be restricted to those patients with a diagnosis of UC only. Data on patient demographics, lifestyle factors, disease duration, disease severity, disease activity, history of prior UC treatment, comorbidities, hospitalizations, adverse events of special interest, medication use, and laboratory results are collected at enrollment and at follow-up visits during routine clinical care. Longitudinal data are obtained via Corrona IBD Questionnaires completed by both patients and their treating gastroenterologists.

The IBD Registry was launched by Corrona in early 2017, with initial Institutional Review Board (IRB) approval occurring on March 24, 2017. As of August 2018, a total of 35 sites have been contracted to participate, with 32 active sites open for enrollment. Of sites approved to enroll, 5 (~16%) are academic and the remaining 27 (84%) are private, community-based sites. Recruiting sites are located across the United States, with representation in 17 states (covering all regions and regional divisions defined by the United States Census Bureau, specifically: Louisiana (LA), Georgia (GA), Maryland (MD), Michigan (MI), Massachusetts (MA), Texas (TX), Florida (FL), Connecticut (CT), Rhode Island (RI), Tennessee (TN), California (CA), Virginia (VA), Nevada (NV), New York (NY), Missouri (MS), Kansas (KS), South Carolina (SC). As of August 2018, over 735 patients have been enrolled across registry sites.

Site selection is based on a number of feasibility and capacity indicators at the sites including available resources to support the study, prior research experience, available patient population, and other site characteristics. Private and academic sites from across the United

States are being recruited for participation in this study. Approximately 100 gastroenterology clinics in the US are expected to provide data for this study; there is no defined upper or lower limit on the number of sites expected to participate. Additional sites may be added if needed to support study recruitment efforts and based on recruitment trends and treatment uptake patterns within the registry, to be evaluated throughout the enrollment period.

9.2.1. Selection criteria

Inclusion criteria

All adult patients (aged 18 years of age or older at index date) who are exposed to tofacitinib for the treatment of UC (identified by clinical disease measures such as the Mayo Score (partial) and the SCCAI) within the Corrona IBD Registry following US launch of the product, will be included in the study. Patients will be identified as incident (i.e., those who start tofacitinib at the time of enrollment in the Corona IBD Registry and have no prior use of tofacitinib) and prevalent users.

There will be two separate comparator populations which will be comprised of:

1. Adult patients (aged 18 years of age or older at index date) exposed to anti-TNF biologics approved for the treatment of UC (e.g. adalimumab, golimumab SC, or infliximab). (Note: The patient population will be stratified by incident and prevalent users. Additionally, a sub-cohort of patients exposed to vedolizumab only may be identified. Rates will be calculated separately for vedolizumab-exposed patients. Formal comparisons [i.e., rate ratios] will be completed if statistical power is achieved in this sub-cohort.)
2. Adult patients (aged 18 years of age or older at index date) exposed only to non-biologic immunosuppressant therapies for treatment of UC (e.g., immunosuppressants such as 6-MP, AZA, tacrolimus, cyclosporine or sulfasalazine), i.e. patients must be naïve to biologic and JAK therapy. (Note: The patient population will be stratified by incident and prevalent users. Formal statistical comparisons [i.e. rate ratios] will be conducted once an appropriate sample size (based on power calculations) is achieved.)

Additionally, to be eligible for enrollment into the Corrona IBD registry, written consent is required independent of this study. Accrual will be monitored throughout the study, and recruitment ratios may be considered to ensure that enrollment into the comparator cohorts are contemporary to tofacitinib enrollment, and to control for potential calendar-time differences between the populations.

Exclusion criteria

1. Patients participating in the Corrona IBD Registry that have a diagnosis other than UC.

2. UC patients participating in the Corrona IBD Registry that are not being treated with tofacitinib or a defined comparator, approved for treatment of UC.

9.3. Variables

Please see Table 1 below. Variables that are routinely collected as part of the Corrona IBD Registry will be included in this study. These include data on clinical assessments of disease activity and severity, comorbidities, past medication use, current medication use, patient demographics (e.g. age, gender, race/ethnicity), lifestyle factors (e.g. history of smoking, alcohol use, disability status), and patient reported outcomes (PROs) which are collected at enrollment from patients and investigators participating in the registry. Changes in these data as well as targeted adverse events (TAE) are collected at routine clinic follow-up visits.

Patient Questionnaires collect patient demographics, lifestyle factors, comorbidities, and PROs, including Health care utilization, PROMIS®, Work Productivity and Activity Impairment.

Provider Questionnaires collect diagnosis, year of onset and diagnosis, comorbidities, infection history, clinical characteristics, disease activity measures, medication use, and adverse events. Blood collection and/or diagnostic evaluations are not required, however, the results are recorded on the Laboratory and Imaging Questionnaire, if obtained.

In addition to the aforementioned variables obtained via routine clinical care, the following sections detail the analytic variables of predominant interest for this study obtained from the investigator and patient enrollment and follow-up questionnaires, and the TAE report forms.

Table 1. Corrona IBD Registry – Key Variables for Inclusion in Safety Study

Variable	Role	Data source(s)	Operational definition
Clinical diagnosis (Ulcerative colitis, Crohn's disease, other indeterminate colitis)	Clinical features	Provider-reported (Enrollment, Follow-up)	Gastroenterologist determination of diagnosis/IBD type
IBD year of onset and diagnosis	Clinical features	Provider-reported (Enrollment, Follow-up)	Year of IBD diagnosis
Height	Clinical features	Provider-reported (Enrollment)	Patient's height in feet, inches
Weight	Clinical features	Provider-reported (Enrollment, Follow-up)	Patient's weight at time of visit (pounds)
Blood pressure	Clinical features	Provider-reported (Enrollment, Follow-up)	Systolic and diastolic blood pressure in mm Hg
Fistula	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of fistula (current or prior)
Pouchitis	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of pouchitis (current or prior)
IBD-related extraintestinal manifestations	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of IBD-related extraintestinal manifestations, specified as applicable
IBD-related surgeries	IBD-related surgeries	Provider-reported (Enrollment, Follow-up)	Presence or absence of IBD-related surgeries (history, since prior visit), with surgery type and date, specified
Resection surgery	IBD-related surgeries	Provider-reported (Enrollment, Follow-up)	Specify locations(s), date(s), total number resections required, and length (cm)

Table 1. Corrona IBD Registry – Key Variables for Inclusion in Safety Study

Variable	Role	Data source(s)	Operational definition
Ostomy surgery	IBD-related surgeries	Provider-reported (Enrollment, Follow-up)	Specify type(s) (takedown, revision, ileostomy, colostomy) and date(s)
Other surgery	IBD-related surgeries	Provider-reported (Enrollment, Follow-up)	Specify other surgery type(s) and dates(s)
Lysis of adhesions	IBD-related surgeries	Provider-reported (Enrollment, Follow-up)	Specify if procedure was required and date completed
Medical History	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of medical conditions or history of events of interest (at time of enrollment), with onset date
History of comorbidities, adverse events, and drug toxicities	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of new onset medical conditions or AEs of special interest with onset date
History of infections	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of (current, prior) infections with onset date and seriousness
Tuberculosis testing	Clinical features	Provider-reported (Enrollment, Follow-up)	Presence or absence of prior testing with test results for standard of care latent or active tuberculosis testing
New Adverse Events, Comorbidities, Drug Toxicities, and Infections	Adverse events	Provider-reported (assessed at Follow-up)	Presence or absence of AEs or new onset comorbidities occurring after enrollment
Simple Clinical Colitis Activity Index (SCCAI)	Disease activity instruments	Provider-reported (assessed at Enrollment, Follow-up)	Score from SCCAI
Mayo Score (partial)	Disease activity instruments	Provider-reported (assessed at Enrollment, Follow-up)	Mayo Score (partial)
Biologics (originators and biosimilars)	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Presence or absence of medication use for treatment of IBD
Small molecules (e.g. tofacitinib)	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Record small molecule drugs in use by patient
Immunosuppressants	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Specific immunosuppressant drugs used for treatment of IBD
Mesalamine	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Specific mesalamine drugs used for treatment of IBD
Antibiotics	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Specific antibiotics used for treatment/management of IBD
Steroids	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Specify steroid use for treatment of IBD
Total Parenteral Nutrition (TPN)	IBD treatments	Provider-reported (assessed at Enrollment, Follow-up)	Specify TPN use for treatment/management of IBD

Table 1. Corrona IBD Registry – Key Variables for Inclusion in Safety Study

Variable	Role	Data source(s)	Operational definition
Dose	IBD treatment	Provider-reported (assessed at Enrollment, Follow-up)	Prescribed dose in medication-appropriate units (g, mg, mg/kg)
Route	IBD treatment	Provider-reported (assessed at Enrollment, Follow-up)	Prescribed, medication-appropriate route of administration
Frequency of administration	IBD treatment	Provider-reported (assessed at Enrollment, Follow-up)	Prescribed frequency of administration
Start date	IBD treatment	Provider-reported (assessed at Enrollment, Follow-up)	Date of drug initiation for specified IBD therapy(ies)
Discontinuation date (or ongoing)	IBD treatment	Provider-reported (assessed at Enrollment, Follow-up)	Date of drug discontinuation or confirmation of ongoing status for specified IBD therapy(ies)
Health insurance	Demographics	Provider-reported (assessed at Enrollment, Follow-up)	Presence or absence of health insurance and type (as applicable)
Year of birth	Demographics	Patient-reported (Enrollment)	Patient's year of birth
Sex	Demographics	Patient-reported (Enrollment)	Patient's self-reported sex
Race	Demographics	Patient-reported (Enrollment)	Patient's self-reported race
Ethnicity	Demographics	Patient-reported (Enrollment)	Patient's ethnicity (Hispanic or non-Hispanic)
Jewish descent	Demographics	Patient-reported (Enrollment)	Patient report of Jewish descent and division (Sephardic, Ashkenazi, Other, Unknown)
Education level	Demographics	Patient-reported (Enrollment, Follow-up)	Highest level of education completed by patient
Work status	Demographics	Patient-reported (Enrollment, Follow-up)	Current primary work status
Marital status	Demographics	Patient-reported (Enrollment, Follow-up)	Current marital status
Medical History	Medical history	Patient-reported (Enrollment)	Specified health conditions and events of special interest with onset (month/year)
Pregnancy history and menopausal status	Patient characteristics	Patient-reported (Enrollment, Follow-up)	History of pregnancy, menopausal status
Disease history of 1st degree relatives	Family history	Patient-reported (Enrollment, Follow-up)	History of IBD (and type) among first degree relatives
Biological children	Patient characteristics	Patient-reported (Enrollment, Follow-up)	Number of biological children, and total number before vs. after diagnosis of IBD
Vaccinations	Vaccination history	Patient-reported (Enrollment, Follow-up)	Vaccinations (new, ever) for HZ, Pneumovax, influenza or HBV and date of most recent vaccination
Smoking and other tobacco use	Lifestyle factors	Patient-reported (Enrollment, Follow-up)	Smoking status (current, prior) with duration and per day cigarette use

Table 1. Corrona IBD Registry – Key Variables for Inclusion in Safety Study

Variable	Role	Data source(s)	Operational definition
Alcohol use	Lifestyle factors	Patient-reported (Enrollment, Follow-up)	Alcohol use (current, prior) with units and frequency
Marijuana use for the treatment of IBD	Lifestyle factors	Patient-reported (Enrollment, Follow-up)	Marijuana use (current, prior) with frequency and primary reason for use
Healthcare utilization	Patient-reported outcomes	Patient-reported (Enrollment, Follow-up)	Presence or absence and total number of hospital admissions or emergency department visits for IBD-related issues in past 12 months (within prior 5 years also assessed on enrollment)
Work Productivity and Impairment (WPAI)	Patient-reported outcomes	Patient-reported (Enrollment, Follow-up)	WPAI score
PROMIS®	Patient-reported outcomes	Patient-reported (Enrollment, Follow-up)	PROMIS score- anxiety, depression, fatigue, sleep disturbance, pain interference
Hematology	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s), and results
Renal function (BUN, Creatinine)	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s), and results
Liver function tests (LFTs)	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s), and results
Inflammatory markers (CRP, ESR)	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s), and results
Lipid panel	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s), and results
Vitamin panel	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s), and results
Fecal	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of recent testing with test date(s), results
Drug concentration and antibody levels	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire (biologics and thiopurine + enzyme activity)	Presence or absence of testing with applicable test date(s), results and units
HBV	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date(s) and results
Capsule endoscopy	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date and results
Histology (cancer, active inflammation, dysplasia)	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date and results
CT or MRI (abscess, active inflammation, fistula)	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of testing with test date and results

Table 1. Corrona IBD Registry – Key Variables for Inclusion in Safety Study

Variable	Role	Data source(s)	Operational definition
DEXA	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of recent DEXA scan with test date and lowest T-score
Mayo Severity Index	Laboratory and Imaging	Laboratory and Imaging Results Questionnaire	Presence or absence of assessment at time of visit with date and score
General Serious Adverse Events (SAEs)	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date
Anaphylaxis or Severe Hypersensitivity Events	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date
Autoimmune Events (new diagnosis)	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date
Cardiovascular Events	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date for serious cardiovascular events
Hepatic Adverse Events	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date for hepatic events that are serious or require liver biopsy
Serious Infection Events	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date for infections meeting SAE criteria or requiring treatment with IV antibiotics
Malignancy Events	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date
Neurologic Events	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date
GI Perforation	Targeted Event	Targeted Adverse Event Questionnaire	Case details including onset date, outcome, clinical details, and resolution date
Pregnancy Event	Targeted Event	Pregnancy Event Questionnaire	Case details including maternal details, assessed pregnancy risks, complications, and outcome
Reason for exit	Study discontinuation	Exit Questionnaire	Specify reason for registry exit (withdrew consent, moved, changed providers, administrative, death)

Table 1. Corrona IBD Registry – Key Variables for Inclusion in Safety Study

Variable	Role	Data source(s)	Operational definition
Exit due to death	Death[1]	Exit Questionnaire	Provider confirmation of death as reason for registry exit
Date of death	Death[1]	Exit Questionnaire	Reported date of death
Primary cause of death (TAE)	Death[1]	Exit Questionnaire	Specify cause of death, TAE details as available
Associated with death (TAE)	Death[1]	Exit Questionnaire	Specify other AEs associated with death, if applicable

[1] Medical records are requested to support confirmation of reported TAE events and deaths
Abbreviations: AE, adverse event; BUN, blood urea nitrogen; cm, centimeters; CRP, C-reactive protein; CT, computerized tomography; DEXA, dual-energy x-ray absorptiometry; e.g., example; ESR, erythrocyte sedimentation rate; g, grams; GI, gastrointestinal; HBV, hepatitis B virus; Hg, mercury; HZ, herpes zoster; IBD, inflammatory bowel disease; IV, intravenous; kg, kilograms; LFTs, liver function tests; mg, milligrams; mm, millimeters; MRI, magnetic resonance imaging; PROMIS, patient-reported outcomes measurement information system; SAE, serious adverse event; SCCAI, Simple Clinical Colitis Activity Index; TAE, targeted adverse event; TPN, total parenteral nutrition; WPAI, work productivity and impairment;

TAE are events of special interest in the registry population (Table 2). Adjudication process for study outcomes of interest is described in Section 9.3.1.

All Serious Adverse Events (SAEs) are reportable on a TAE Questionnaire, for the purposes of this registry.

Table 2. Flagged Events Reportable on Targeted Adverse Event Questionnaires in the Corrona IBD Registry

Flagged Event (□)	TAE Questionnaire
Serious hypertension event	**CARDIOVASCULAR**
Cardiac revascularization procedure (CABG, stent, angioplasty)	
Ventricular arrhythmia	
Cardiac arrest	
Myocardial Infarction	
Acute Coronary Syndrome	
Unstable angina	
Congestive heart failure	
Stroke	
Transient ischemic attack	
Deep vein thrombosis	
Pulmonary embolism	
Other (serious) cardiovascular condition (specify)	
Colon cancer	**MALIGNANCY**
Colonic dysplasia	
Lymphoma	
Lung cancer	
Breast cancer	
Skin cancer (melanoma)	
Skin cancer (basal cell)	
Skin cancer (squamous cell)	
Other cancer (specify)	
Alopecia areata	**AUTOIMMUNE**
Alopecia totalis	
Autoimmune hepatitis	
Psoriasis	
Sarcoidosis	

Table 2. Flagged Events Reportable on Targeted Adverse Event Questionnaires in the Corrona IBD Registry

Flagged Event (□)	TAE Questionnaire
Sjogren's syndrome	
Vasculitis	
Progressive Multifocal Leukoencephalopathy (PML)	**NEUROLOGIC**
Demyelinating disease	
Multiple sclerosis	
Other Neurological disorder (serious)	
Drug-induced hypersensitivity reaction (Severe hypersensitivity reaction or Anaphylaxis)	**DRUG-INDUCED HYPERSENSITIVITY/ REACTIONS**
Infections that are serious[1] and/or require treatment with IV antibiotic (as an outpatient)	**SERIOUS INFECTIONS**
Hepatic adverse events (serious or requiring biopsy)	**HEPATIC**

1 Serious events are defined as resulting in any of the following outcomes: hospitalization (new or prolonged), death, immediately life threatening (requiring urgent intervention to prevent death), significant or persistent disability or incapacity, congenital anomaly/birth defect, or an otherwise serious medically important event in the opinion of the Investigator).
2 The General Serious Targeted Adverse Event Questionnaire should be used to report serious events that are not reportable under a more specific Targeted Adverse Event type/category
Abbreviations: CABG, coronary artery bypass graft; IV, intravenous; TAE, targeted adverse event;

Information about pregnancies and their outcomes is collected via the Pregnancy Event Questionnaire, initially completed at the time the site is made aware of a pregnancy (occurring in a participating female patient) and updated continuously as new information and pregnancy-related outcomes become known. Data on partners of male patients will not be available.

Study outcomes and exposures are described in detail in the subsequent sections.

9.3.1. Study Outcomes

The Corrona IBD registry utilizes an established data collection system for detecting and evaluating TAEs.

Primary comparative analyses will include physician-reported endpoints (fulfilling minimum case reporting criteria, i.e. identifiable: patient, reporter, event, and medicinal product) that have been reported via Provider Follow-up, TAE, and/or Exit forms (excluding physician-reported endpoints that have later been revoked or determined to be duplicate reports). Secondary analyses will only include those physician-reported endpoints that have been adjudicated as endpoint met (i.e. definite, probable, or possible). Physician-reported endpoints for which adequate supporting source documents are not available are not eligible for adjudication.

The Corrona registry model is an efficient data collection system for evaluating a range of safety outcomes associated with therapies used to treat UC including malignancy, MACE, and serious infections. Prior post-approval validation studies have been completed (and described) assessing rates of observed endpoints including malignancy, MACE, and serious infections reported in registry participants[3,4,5].

The primary outcome under study is malignancy, excluding NMSC. Secondary outcomes include NMSC, MACE, opportunistic infections (e.g. tuberculosis, opportunistic mycoses), HZ reactivation, PML, SIEs, venous thromboembolic events (DVT and PE), hepatic adverse events (serious or requiring liver biopsy), GI perforations, surgery for UC and all-cause mortality. The following sections describe each outcome as captured by the Corrona IBD Registry, with discussion on outcome analyses in Section 9.7.

9.3.1.1. Malignancy, Excluding NMSC

The primary outcome being examined in this study is malignancy (excluding NMSC).

Cases of malignancy are captured by Provider Follow-up and TAE Questionnaires and include skin cancers, solid cancers, and hematologic cancers. Specific subtypes of interest include colorectal, lymphomas, pulmonary, breast, and melanoma skin cancers.

Validation of incident malignancies within the Corrona RA Registry has been described previously, and is the same process implemented within the Corrona IBD Registry[3]. Malignancy events are reported by investigators who are required to complete a TAE Questionnaire for each report of incident malignancy. Sites are required to request source documentation to support event confirmation, including but not limited to biopsy/pathology reports or other relevant confirmatory test results, oncologist notes, hospital discharge summaries, and death certificates, if applicable. Each case with sufficient supporting records available will be adjudicated and classified as definite, probable, possible or not an event via case review and endpoint evaluation by trained medical reviewers. Secondary analyses for the endpoint of malignancy (excluding NMSC) will include all events adjudicated as definite, probable, or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.2. NMSC

One of the secondary outcomes being examined in this study is NMSC.

The occurrence of NMSC is collected via Provider Follow-up and TAE Questionnaires. Validation of NMSC follows the same process as the malignancies described above (Section 9.3.1.1).

9.3.1.3. Serious Infections

A secondary outcome being examined in this study is the occurrence of SIEs. The occurrence of SIEs is collected via the Provider Follow-up and TAE Questionnaires. SIEs include infections meeting serious adverse event criteria[6] and/or requiring treatment with intravenous (IV) antibiotics. The Corrona IBD Registry requires gastroenterologists to complete the TAE form and request source documentation so that physician-reported SIEs with sufficient supporting records available can be adjudicated and classified as definite, probable (empirically treated), possible and not an event. Secondary analyses for the endpoint of SIE will include all events adjudicated as definite, probable (empirically treated), or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.4. Opportunistic Infections

This study will examine serious infections and all opportunistic infections. Opportunistic infections will be identified using pathogen indicators as defined in Winthrop KL, et al. [15] The occurrence of opportunistic infection is collected via Provider Follow-up and TAE Questionnaires. Serious opportunistic infections identified from TAE forms will be defined as those meeting criteria for reporting as a Serious Adverse Event, or requiring treatment with IV antibiotics as an outpatient. Non-serious opportunistic infections are collected via investigator Follow-up Questionnaires. Both serious and non serious infections require capture of minimum data elements to support event characterization, including the organism(s)/pathogen(s) identified via confirmatory testing (as applicable) for reported infections. TAE forms and supporting documentation corresponding with serious opportunistic infections with sufficient supporting records will be validated and confirmed via case review and endpoint evaluation by trained medical reviewers. Serious opportunistic infections will be adjudicated and classified as definite, probable (empirically treated), possible, or not an event. Secondary analyses for the endpoint of opportunistic infections will include all events adjudicated as definite, probable (empirically treated), or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.5. Herpes Zoster Reactivation

The occurrence of herpes zoster events is collected via the Provider Follow-up Questionnaire. The Corrona IBD Registry requires gastroenterologists to report cases of HZ in the Provider Follow-up Questionnaires (for serious and non-serious) and TAE form and request source documentation for cases of serious HZ. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated or included in secondary analyses of adjudicated endpoints. Herpes zoster events will be adjudicated and classified as definite, probable (empirically treated), possible, or not an event. Secondary analyses for the endpoint of herpes zoster will include all events adjudicated as definite, probable (empirically treated), or possible by the registry adjudication committee.

9.3.1.6. Venous Thromboembolic Events

The occurrence of thromboembolic events (DVT and PE) is collected via Provider Follow-up and TAE Questionnaires. The Corrona IBD Registry requires gastroenterologists to complete the TAE form and request source documentation so that physician-reported thromboembolic events with sufficient supporting documentation available can be adjudicated and classified as definite, probable, possible and not an event. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated. Secondary analyses for the endpoint of thromboembolic events will include all events adjudicated as definite, probable, or possible by the registry adjudication committee.

9.3.1.7. Major Adverse Cardiac Events

The occurrence of MACE is collected via Provider Follow-up and TAE Questionnaires. The Corrona registry requests additional clinical information on physician-reported MACE

events. The Corrona IBD Registry requires gastroenterologists to complete the TAE form and request source documentation so that physician reported MACE events [myocardial infarction, stroke, cardiovascular (CV) death] with sufficient supporting documentation available can be adjudicated and classified as definite, probable, possible and not an event. Secondary analyses for the endpoint of MACE will include all events adjudicated as definite, probable, or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.8. Hepatic Events

The occurrence of hepatic events classified as a serious adverse event and/or required a liver biopsy are collected via the Provider Follow-up and TAE Questionnaires. The Corrona IBD Registry requires gastroenterologists to complete the TAE form and request source documentation so that physician-reported hepatic events with sufficient supporting documentation available can be adjudicated and classified as definite, probable, possible, or not an event. Secondary analyses for the endpoint of hepatic events will include all events adjudicated as definite, probable, or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.9. GI Perforation

The occurrence of a GI perforation is collected via Provider Follow-up and TAE Questionnaires. The Corrona IBD Registry requires gastroenterologists to complete the TAE form and request source documentation so that physician-reported GI perforation events with sufficient supporting documentation available can be adjudicated and classified as definite, probable, possible, or not an event. Secondary analyses for the endpoint of GI perforation will include all events adjudicated as definite, probable, or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.10. Progressive Multifocal Leukoencephalopathy

The occurrence of PML is collected via Provider Follow-up and TAE Questionnaires. The Corrona IBD registry requires gastroenterologists to complete the TAE form and request source documentation so that PML events with sufficient supporting documentation available can be adjudicated and classified as definite, probable, possible, or not an event. Secondary analyses for the endpoint of PML will include all events adjudicated as definite, probable, or possible by the registry adjudication committee. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.11. All-cause Mortality

The Corrona registry captures supplemental clinical information on physician-reported deaths and/or TAEs with an outcome of death. The occurrence of death is collected via the Exit, and TAE Questionnaires. The registry requires gastroenterologists to complete Exit and

TAE forms and request source documentation (where applicable) so that physician-reported events with sufficient supporting documentation available can be adjudicated to confirm site-reported details including cause of death, associated AEs and date of death. Reported causes of death will be classified as definite, probable, possible, or not able to confirm as cause of death. Secondary analyses for the endpoint of death will include all events (with available cause of death information) adjudicated as definite, probable, or possible by the registry adjudication committee. Deaths (and corresponding TAEs) that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

9.3.1.12. Surgical Procedures for Management of UC

The Corrona IBD registry captures clinical information on surgeries for treatment/management of IBD from the Provider Follow-up Questionnaire. Surgeries requiring overnight hospitalization or otherwise meeting serious adverse event criteria are reported in additional detail using the General Serious TAE Questionnaire. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated or included in secondary analyses of adjudicated endpoints.

9.3.2. Corrona IBD Registry Safety Endpoint Procedures

The Corrona IBD Registry utilizes an established data collection system for detecting and evaluating Targeted Events (i.e., adverse events or endpoints of special interest).

Primary analyses for this study will include all confirmed endpoints via a combination of physician report and follow-up TAE forms. Secondary analyses will include adjudication of events that are complete with source documentation.

Within the Corrona IBD Registry, TAE Questionnaires are requested for any “flagged events” (see Table 2) reported via the Corrona Provider Follow-up or Exit Questionnaires. Supporting documentation that are appropriate to event type (e.g., hospital discharge summaries, biopsy results, consultant notes) are requested for targeted events that the gastroenterology provider becomes aware of during the course of the registry. This process can be summarized as follows:

- Site reports a flagged event on registry follow-up questionnaire.
- Corrona’s data capture system generates a Targeted Event form for event confirmation and completion of supplemental details by the site. Sites are prompted to provide supporting documents as per the Minimum Supporting Documentation by TAE Type guidelines for registry sites (see Appendix 1).
- Corrona Pharmacovigilance completes clinical review of submitted event details and supporting documentation, following up with the site as needed, to validate the event.

All Targeted Event Questionnaires include standardized questions including assessment of seriousness and serious criteria fulfilled[6]. All confirmed SAEs are reportable to Corrona on a TAE Questionnaire. Event outcome is collected in all Corrona Targeted Event Questionnaires. Sites are instructed to follow-up on reported Targeted Events until outcome resolution, where status is recorded as ongoing at the time of initial report.

Physician-reported adverse events fulfilling minimum case reporting criteria, i.e. identifiable: patient, reporter, event, and medicinal product that have later been revoked or determined to be duplicate reports will be considered cases for purposes of inclusion in the primary analyses. As per the Corrona IBD Registry protocol, participating sites are required to make attempts to obtain appropriate medical records in support of reported Targeted Event and to document a valid reason where records are not able to be obtained to support formal adjudication, despite efforts made by the site. TAEs that are not complete with supporting documentation, or for which supporting documentation has been deemed insufficient to support confirmation of the reported event will not be adjudicated.

Sensitivity analyses will be conducted to ascertain differences in incidence rates observed in adjudicated (primary and secondary) endpoints compared with physician-reported (physician-reported events that have not later been revoked or determined to be duplicate reports) for the same events. For the primary and secondary endpoints of interest, physician-reported events with supporting documents (i.e. medical records) are triaged for clinical review by trained and medically qualified specialists to confirm site-reported details including: reported event term(s), date of event onset, and whether the endpoint in question was met in the opinion of the adjudicator.

9.3.3. Drug Exposure

Patients can already be on therapy or starting new therapy at time of enrollment. As a result, new therapy users (incident users) and continuing therapy users (prevalent users) are captured in the registry (Figure 1).

Time at risk for incident users will begin at the start of drug exposure. Incident users include patients that initiate tofacitinib or a comparator at the time of enrollment into the IBD registry, as well as patients that switch to tofacitinib or a comparator at the time of a registry follow-up visit. Sites enrolled within the Corrona IBD Registry are trained to complete registry Follow-up Questionnaires at the time of new biologic switch, regardless of whether the patient is due for their next registry follow-up (the follow-up schedule is reset from the date of the new biologic switch).

Prevalent users are defined as patients who have initiated therapy with tofacitinib or a comparator during the 12 months prior to registry enrollment (those patients who have initiated therapy more than 12 months prior to registry enrollment are not eligible for enrollment into the registry). Prevalent users will be included in this study in order to balance two major considerations: 1) achievement of recruitment goals within the expected time-frame (particularly as the Corrona IBD Registry is a newer registry that does not have a large cohort of previously enrolled patients); and 2) restricting the prevalent users to a recent switch and date since drug initiation, since there is the anticipation that tofacitinib patients will be enrolled closer to their drug start (versus the potential for patients who have been on anti-TNF therapy for multiple years). Thus, by applying these criteria, this approach will substantially reduce any imbalances in the duration on therapy for prevalent users between tofacitinib and comparators (all patients will be either new starts or would have started therapy within 12 months of registry enrollment).

Time at risk for prevalent users will begin from the date of enrollment. Prevalent users will contribute exposure time and adverse events occurring after the date of enrollment and within the defined risk windows for tofacitinib and comparators based on event type. Limiting the duration of therapy at time of enrollment for prevalent users is intended to minimize imbalances in duration of therapy between the groups and maximize timely availability of data to support primary analyses and examination of other mid to long range outcomes. Any safety events that occur prior to enrollment, but after initiating therapy among prevalent users will be collected as medical history, and will be accounted for in multivariate regression analysis.

Sensitivity analyses will be completed to examine whether differences are observed in rates when restricting to an incident user population.

Figure 1. Incident and Prevalent Users

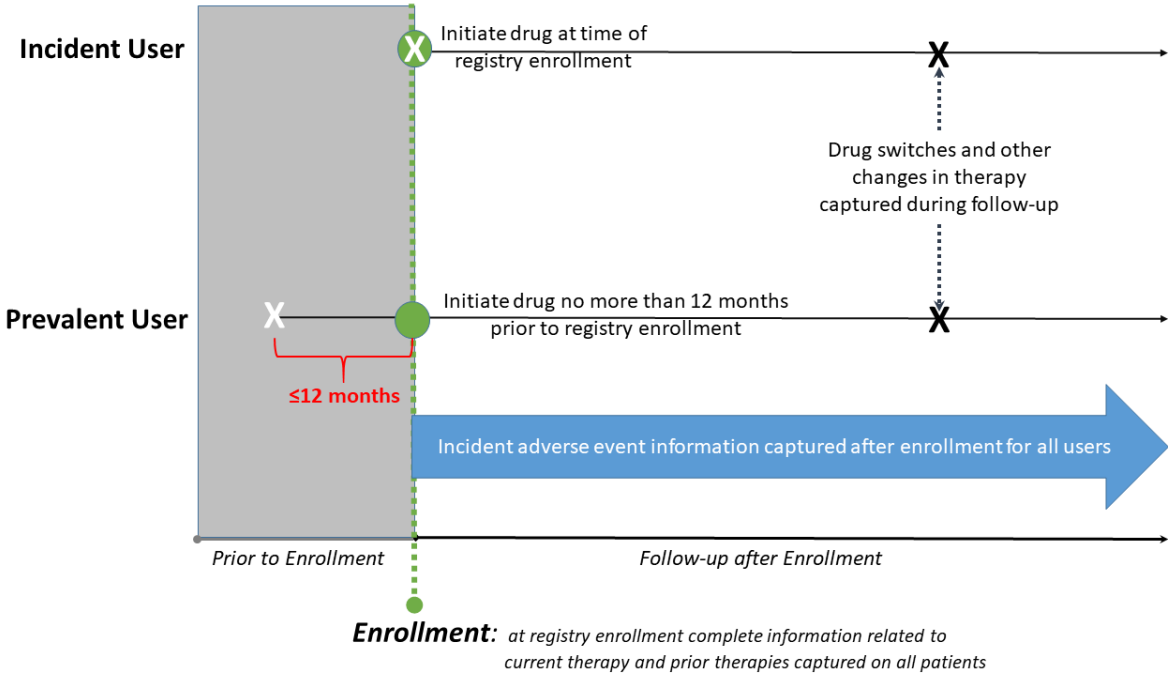


Table 3 displays medications captured for UC in the IBD Registry. Newly available UC medications will be reviewed and accepted based on FDA approval. Once a patient is enrolled into the registry, follow-up will occur regardless of the UC treatment received. Therefore, it is possible for a patient to have exposure to a drug during the course of the registry that is not part of the eligible medications for registry enrollment (e.g. non-FDA approved biologics, other non-biologics immunosuppressant systemics, and small molecule therapies approved for use in UC). This potential confounding factor in the evaluation of the data will be accounted for in a Statistical Analysis Plan (SAP). All drug utilization data will be collected at each study visit.

Table 3. Medications for UC Treatment Currently Captured in the Corrona IBD Registry by Cohort

Non-Biologic Systemic (Immunosuppressant) Medications (NBSM)		Biologic Medications		JAK inhibitors
sulfasalazine	**tacrolimus**	**adalimumab (anti-TNF)**	**golimumab (anti-TNF; Simponi subcutaneous formulation)**	**tofacitinib**
cyclosporine	**azathioprine**	**infliximab (anti-TNF)**	**Vedolizumab**	
6 mercaptopurine	balsalazide	certolizumab pegol (anti-TNF)	Natalizumab	
		ustekinumab		

Drugs in **bold** are currently used in UC

NBSM = non-biologic systemic medications; TNF = tumor necrosis factor

The classification of drug exposure within this study differs for the evaluation of the primary outcome malignancy compared to other (secondary) outcomes to accommodate the long latency of malignant outcomes even after a causal exposure (meaning even when causality or attribution is clear/known, as in asbestos exposure for example, there is a latency period from exposure to onset) (Section 9.3.3.1). In order to accommodate the long latency that would be expected for any malignant outcomes that might occur after an exposure, exposure assignment for malignancies will be a once-exposed-always-exposed approach. The risk window for any therapy (tofacitinib, biologic comparator or immunosuppressant comparator) will include all person-time in the designated time period (since starting first therapy in a particular therapy group) and extend until the end of data collection, even in the case of subsequent switching to another agent in another therapy group. When a malignancy is diagnosed, any drug group that the patient has been exposed to prior to the incident malignancy in this study will receive attribution in the incidence rate estimations.

The secondary outcomes of NMSC and death will be an exception to the other secondary outcomes, as these will also follow the same analytical once-exposed-always-exposed grouping and methods as the primary malignancies. For the remaining secondary outcomes other than NMSC and death, an “as-treated” approach will be used instead, where person-time accrues simply based on the treatment received.

Before analyses occur, drug exposure patterns will be examined to ensure that pre-defined exposure cohorts accurately represent exposure in the general population, as reflected by periodic inspection of real-world patterns of use in Corrona and other available data sources. As this is an observational registry, Corrona cannot require that patients remain on drug for a specified amount of time. However, based on data from. the Corrona Rheumatoid Arthritis Registry showing thatamong those with at least 18 months of registry follow-up after a tofacitinib initiation, 56% of patients remained on drug for at least 18 months, it is anticipated that a substantial proportion of UC patients will remain on tofacitinib for at least 18 months after initiation. For primary and secondary analyses, drugs in the same class as tofacitinib (i.e. JAK inhibitors) that may come on the market during the study period will be excluded from all exposure cohorts to control for potential confounding factors (potential class effects) among tofacitinib or comparator cohorts.

9.3.3.1. Drug Exposure and Cohort Identification for Malignancy Outcomes

For the primary outcome of malignancy excluding NMSC and secondary outcomes NMSC and death, follow-up time will be categorized into three exposure groups or cohorts: tofacitinib, anti-TNF biologic therapy, and immunosuppressant non-biologic systemic medication (NBSM) therapies. In order to accommodate the long latency that would be expected for any malignant outcomes that might occur after an exposure, exposure assignment for evaluating malignancies will be a once-exposed-always-exposed approach to attribution of malignancy events.

Specifically, once exposure to tofacitinib occurs, exposure time will continue even in the case of subsequent switching to a different drug in another therapy group until the first malignancy or death event, or until the end of the data collection period; once exposure to anti-TNF biologic therapy occurs, exposure time will also continue even in the case of subsequent switching to a different drug in another therapy group until the first malignancy

or death event, or until the end of the data collection period; for the non-biologic immunosuppressant group that is naïve to tofacitinib and biologics by definition, time is assigned to the respective group. In the event of a switch, exposure time for the new therapy would begin at time of switch and continue until first malignancy/death, or until end of study. Using the once-exposed, always-exposed approach, an individual may contribute exposure time and events to multiple exposure cohorts.

For example, for patients with exposure to anti-TNF biologic therapy who subsequently switch to tofacitinib therapy, when a malignancy is diagnosed, exposure time and events will be attributed to both anti-TNF biologic group and tofacitinib group. The risk window for the anti-TNF biologic will be from time of initiation of the anti-TNF biologic until the malignancy, irrespective of the switch to tofacitinib. For tofacitinib, the risk window will be from time of tofacitinib initiation (time of switch to tofacitinib) until the malignancy.

The three medication cohorts are further described below.

- **Tofacitinib cohort:** Patients exposed to tofacitinib with no prior exposure to a non-tofacitinib JAK inhibitor; exposure time will begin at registry enrollment (if patient is a prevalent user or incident user of tofacitinib at time of enrollment) or subsequent treatment initiation (switch to tofacitinib from another drug during follow-up) and will continue until end of the study period, withdrawal from the registry, incident malignancy, or death; new and continuing user status will be updated at each time point.
- **Anti-TNF biologic cohort:** Patients using an anti-TNF biologic medication without previous exposure to a JAK inhibitor; follow-up will begin at registry enrollment (if patient is a prevalent user or incident user of anti-TNF biologic at time of enrollment) or subsequent treatment initiation (if patient enrolls into registry as NBSM user) and will continue until end of the study period, withdrawal from the registry, incident malignancy, or death; continuing user status will be updated with additional switches to subsequent anti-TNF biologics.
- **NBSM (Non-Biologic Systemic Medication) Immunosuppressant cohort:** Biologic-naïve immunosuppressant NBSM users; follow-up time will begin at registry enrollment and continue until end of the study period, withdrawal from the registry, incident malignancy, or death; continuing user status will be updated with subsequent switches to other NBSM drugs.

If a patient is exposed simultaneously to anti-TNF biologic and NBSM immunosuppressant therapy, this time will be assigned only to the anti-TNF biologic cohort. The once-exposed-always-exposed approach will also be used for the secondary outcomes of NMSC and death.

9.3.3.2. Drug Exposure and Cohort Identification for Non-Malignancy Outcomes

Unlike for malignancies (including the secondary outcomes NMSC and death), the remaining secondary outcomes of MACE events, opportunistic infections, herpes zoster, PML, SIEs, thromboembolic events (DVT and PE), hepatic adverse events (serious or requiring liver biopsy), GI perforation, and surgery for UC are expected to occur in closer proximity to any presumptive causal exposure, and so the classification of exposures would be represented by change in those exposures. As a result, exposure will be classified using an “as-treated” approach while utilizing the same 3 cohorts described in Section 9.3.3.1. Using the “as-

treated" approach, person-time will accrue based on the treatment received and will reflect actual confirmed use during each *medication episode*.

A 90-day risk window will be added to the end of the treatment period[7,8,9,10] for tofacitinib and comparators. During this window, patients continue to accrue "time at risk" for 90 days after the medication is stopped.

- **Tofacitinib cohort**: Patients initiating tofacitinib; exposure time will begin at treatment initiation and will continue until either the occurrence of an event, medication discontinuation (plus 90 days), switch to another JAK (for those approved after study start), switch to a biologic medication, withdrawal from the registry, or death; a new index date will be assigned when a patient switches medication; concomitant use of a NBSM will be assessed and included in the analysis as a time-dependent covariate.
- **Anti-TNF biologic cohort**: Patients initiating an anti-TNF biologic medication approved for the treatment of UC; follow-up will begin at treatment initiation and will continue until either the occurrence of an event, medication discontinuation (plus 90 days), switch to tofacitinib or another JAK, switch to another biologic medication, withdrawal from the registry, or death; a new index date will be assigned when a patient switches medication; concomitant use of a NBSM will be assessed and included in the analysis as a time-dependent covariate.
- **NBSM Immunosuppressant cohort**: Biologic-naïve NBSM users; follow-up time will begin at NBSM initiation and will continue until either the occurrence of an event, medication discontinuation (plus 90 days), initiation of a biologic medication, tofacitinib or another JAK (for those approved after study start), withdrawal from the registry, or death; a new index date will be assigned when a patient switches medication.

Simultaneous use of biologic medications is expected to be rare, as current treatment guidelines do not recommend the use of multiple biologic medications concurrently[11]. Details of how this will be handled statistically, should it occur, will be described in the SAP; however, such patients may either be excluded or exposures can be assigned to all relevant groups, without double counting if concurrent therapies are within the same group. Exposure time for patients with simultaneous use of tofacitinib and a biologic concomitantly, should it occur, will be assigned to the tofacitinib cohort. Medications currently considered for the anti-TNF biologic concomitant use include adalimumab, infliximab, and golimumab (Simponi, sub-cutaneous formulation) (Table 3) with future anti-TNF biologics and biosimilars to be added as they are approved for use in UC. A patient will only be defined as initiating a biosimilar if the patient has had no prior exposure to the originator drug. If a patient is exposed simultaneously to biologic and NBSM immunosuppressant therapy, this time will be assigned only to the anti-TNF biologic cohort.

9.3.4. Exposure Classification

Corrona IBD Registry patients receive routine clinical care that affects the patterns of treatments after enrollment. These patterns, and in particular the switching of medications during the study, result in switching within and between the study-defined-specific

medication exposure cohorts. Follow-up time attribution for patients with varying medication patterns may affect factors that confound the relationship between exposure and outcome factors collected at treatment initiation (i.e. *index date*) and at follow-up visits, e.g., smoking in a malignancy analysis. This information is used in the propensity score matching described in Section 9.7 to help ensure that confounding factors are evenly distributed, or balanced, across exposure cohorts being compared.

Each patient in the registry is assigned the index date for treatment initiation representing the start of the observation period where the patient begins contributing person-time to the specified exposure cohorts for the study. When a patient switches medication *within an exposure cohort*, a new index date is assigned and they are re-matched with another initiator in the comparator cohort. The alternative would be for the original patient who switched medication to remain matched to a continuing user of the previous medication, which would preclude robustness (including sufficient overlap and common support).

Follow-up time will be measured from the index date to the occurrence of an event (for a time-to-event analysis), death, medication discontinuation, *initiation of a medication for another exposure cohort*, or the last follow-up visit.

For tofacitinib initiators or anti-TNF biologic users (when evaluating non-malignancy outcomes), a 90-day period following the end of a period of medication use will be added to the time at risk for that medication. 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. Any event prior to the new medication start will be assigned to the discontinued medication. A 90-day risk window was selected for TAEs except malignancy and death based on published literature[8,9,10] that frequently applied a 90-day window (a conservative approach to ensure that multiple half-lives after drug discontinuation are part of the risk window). This is true for the majority of UC advanced therapies, although half-lives vary by advanced therapy.

A sensitivity analysis will be completed to determine whether incidence rates or distributions of secondary outcomes differ significantly when applying a risk window of 30 days, when compared with the 90-day period, applied to the treatment discontinuation date.

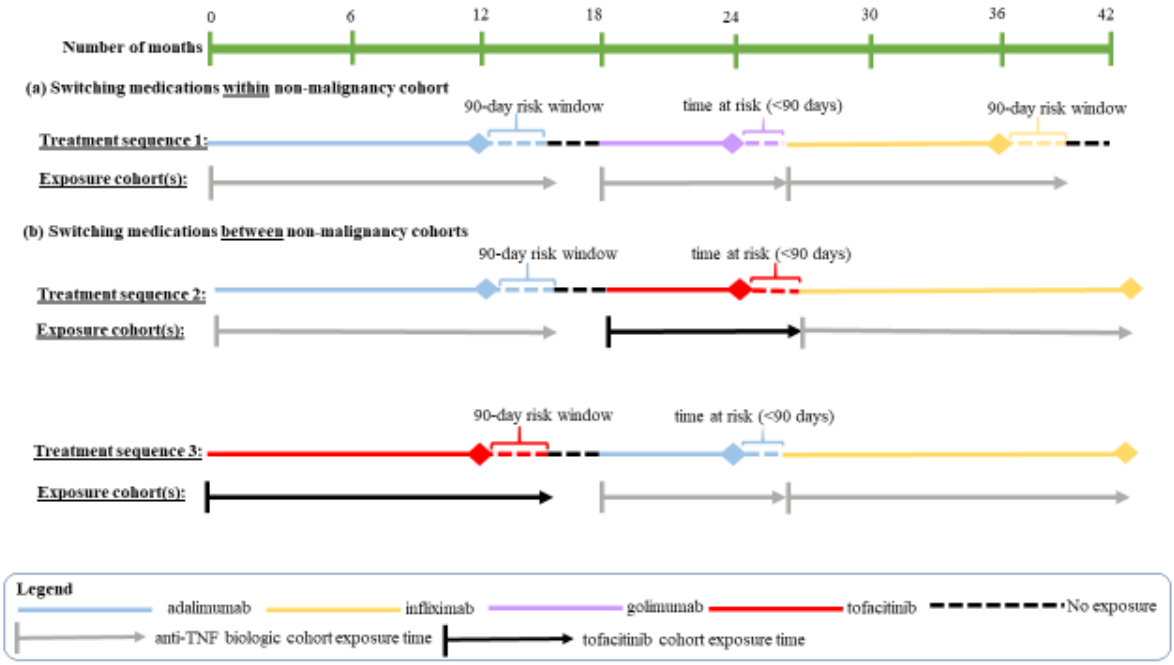
9.3.4.1. Switching

9.3.4.1.1 Switching within medication cohorts (Figure 2, Part a)

Figure 2, Part a (below) illustrates a patient who initiates adalimumab treatment at the start of the registry and continues until Month 12. The 90-day risk window is added to the adalimumab exposure time, for a total of 15 months of person-time being contributed (added) to the accumulated person time for the anti-TNF biologic cohort. At Month 18, the patient initiates golimumab and continues until Month 24 (6 months of person-time). The golimumab at-risk window continues until the start of infliximab at Month 26, resulting in 8 months of person-time contributed to golimumab. At Month 26, the patient initiates infliximab and continues until Month 36, for a total of 13 months of infliximab exposure, including the 90-day risk window. By the end of this observation period, this patient will contribute 36 months of person-time in total to the biologic group (15 months of adalimumab, 8 months of golimumab, and 13 months of infliximab).

Figure 3 displays the exposure contributions had this been an analysis of malignancy. Treatment Sequence 1 results in a total of 42 months of exposure time contributed to the anti-TNF biologic cohort since all follow-up time following the first anti-TNF biologic initiation contributes to the anti-TNF biologic cohort.

Figure 2. Example of Exposure Classification – Switches within non-malignancy cohorts and switches between non-malignancy cohorts



9.3.4.1.2 Switching between medication cohorts (Figure 2, Part b)

Switching between medication cohorts may also occur and will be managed similarly to the within-medication cohort switch described above. This scenario is illustrated in Figure 2, Part b.

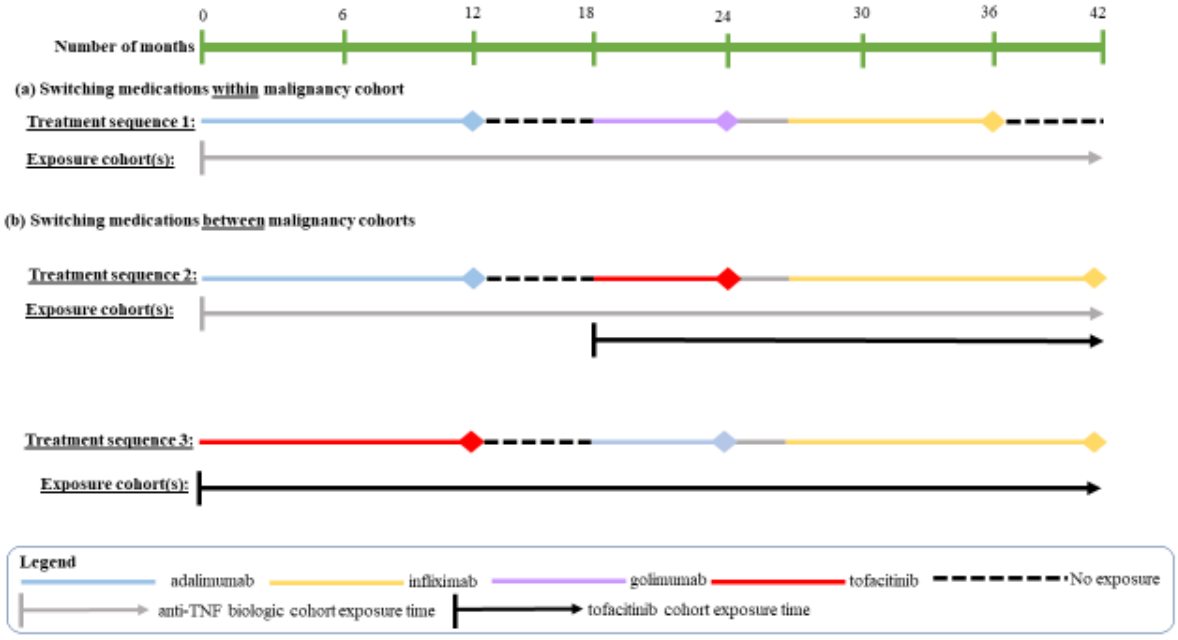
In the Treatment Sequence 2, assume an analysis for a non-malignancy outcome so exposures are assigned "as-treated" rather than following a once-exposed-always-exposed approach. Just as for switching within a cohort, this patient initiates treatment with adalimumab at the start of the registry and continues treatment until Month 12. After the 90-day risk window is added, 15 months of person-time is contributed to the anti-TNF biologic cohort (adalimumab exposure). At Month 18, the patient switches to tofacitinib and continues until Month 24 and now contribute to the tofacitinib cohort until the initiation of infliximab at Month 26 (a total of 8 months contributed to the tofacitinib exposure cohort). At Month 26, the patient initiates infliximab and continues on treatment up to the end of the observation period at Month 42, for a total of 16 months of infliximab exposure and a total of 31 months in the biologic group (15 months of adalimimab and 16 months of golimumab). In Treatment Sequence 3, although the patient receives tofacitinib prior to anti-TNF biologic therapy, the patient contributes exposure time to both the tofacitinib and anti-TNF biologic

cohorts: 15 months tofacitinib, 24 months anti-TNF biologic cohort (8 months adalimumab, 16 months infliximab).

Figure 3 displays the exposure contributions had this been an analysis of malignancy. In Treatment Sequence 2, the patient would contribute 42 months to the anti-TNF biologic cohort, and would contribute 24 months to the tofacitinib cohort. In treatment Sequence 3, the patient would contribute 42 months of exposure time to the tofacitinib cohort. There is not contribution to the anti-TNF cohort in Treatment Sequence 3 due to the prior exposure to a JAK inhibitor at the time of anti-TNF biologic initiation.

In addition, if the primary analysis reveals a significant result, either in favor of tofacitinib or the comparator, a sensitivity analysis will be conducted assessing time since initiation of index medication, allowing for latency periods. For example, analyses will be conducted such that only patients with at least 6 months of drug exposure will be included. Only new initiators will be considered for the analysis.

Figure 3. Example of Exposure Classification for Malignancy



9.3.5. Medication Restarts

During the course of follow-up, patients may stop and restart medications at the discretion of the investigator. Medication restarts captured within the registry will not affect the analysis of the primary outcome (malignancy), as the analytic approach for malignancies considers ever-exposure versus never-exposure to tofacitinib.

However, treatment episodes that include medication restarts will affect the analysis of secondary outcomes. Patients restarting medications may have a different risk for study outcomes relative to patients who initiate or continue treatment. Therefore, patient characteristics and risk of study outcomes 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 important 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 and will be matched to a similar re-starter in the comparison exposure cohort.

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

9.4. Data sources

9.4.1. Corrona IBD Registry Questionnaires

Physicians and patients complete Corrona Data Collection Program Questionnaires approximately every 6 months. During the course of a regularly-scheduled office visit, the physician performs assessments as mandated on the Corrona Registry Provider Questionnaires with recording of pertinent data. Results from certain standard of care laboratory tests (e.g. CBC, chemistry, lipid and/or inflammatory marker panels) are included and collected as available, but testing is not mandated, on these Questionnaires. Patients are asked to complete Questionnaires designed to capture information ranging from their general demographics and experience with prescription drug use to an overall global assessment of their disease. During their regularly-scheduled physician office visits, it is anticipated that patients will spend approximately five to ten minutes completing the Questionnaires. Neither the Questionnaires completed by providers nor the Questionnaires completed by patients contain patients' names, addresses, telephone numbers, email addresses, or social security numbers.

Patients are enrolled in the Corrona IBD Registry during regularly-scheduled office visits. Upon enrollment, physicians complete a Provider Enrollment Questionnaire that includes a Simple Clinical Colitis Activity Index (SCCAI), pouchitis history and a Mayo score (partial). Patients also complete an Enrollment Questionnaire that includes questions about Healthcare Utilization, the Patient-Reported Outcomes Measurement Information System (PROMIS®) and the Work Productivity and Activity Impairment questionnaire (WPAI).

After the enrollment visit, patients then complete Corrona IBD Registry Follow-up Questionnaires during regularly scheduled clinical encounters approximately every 6 months.

Data are collected on patients for as long as they consent to remain in the registry.

9.4.2. Study Patient Exit

In the event of a patient death, withdrawal from the registry loss to follow-up (for patients the site is unable to reestablish contact with or confirm vital status despite documented attempts),

or administrative exit (defined as no registry visits completed or TAEs have occurred in the previous 15 months of real-world observation), or any other reason for non-participation, the Patient Exit Questionnaire is to be completed by the provider and submitted according to the submission procedures provided to the site by the Corrona Organization.

9.4.3. Targeted Adverse Event (TAE) Questionnaires

Adverse events which occur during participation in the registry's Data Collection program are reported on the TAE Questionnaires. TAE Questionnaires are completed and submitted when a flagged event on a Corrona Data Collection Program Provider Follow-up Questionnaire has been selected. Submission of de-identified source documents (i.e. hospital records, laboratory results, etc.) in support of the reported TAE is required in order to be valid, unless otherwise determined by the Corrona Organization. The TAE should be simultaneously reported on both the TAE Questionnaire and on the Corrona Data Collection Program Provider Follow-up Questionnaire visit date that most closely follows the event (unless the TAE occurs on the date of the Follow-up Visit).

Details regarding requirements for reporting serious adverse events occurring in patients being treated within the defined exposure windows for tofacitinib will be reported by Corrona to Pfizer, as further detailed in Section 11, below.

9.5. Study size

This safety study is powered to define the minimal sample size required to detect a 1.8-fold increase in relative risk using a 0.60 per 100 patient-years incidence rate for the primary outcome of malignancy, excluding NMSC for the comparator group. This conservative incidence rate was derived after evaluating differing sources of information, including published literature for a range of incidence rates from 0.77 to 0.92[12,13,14]. Current incidence rate estimates from the Corrona rheumatoid arthritis (RA) cohort were also considered, which were 0.84 per 100 person-years for biologic-exposed RA patients and 0.73 per 100 person-years if this RA cohort was restricted to those on drug for at least 6 months.

A sample size of 1143 patients in the tofacitinib cohort and 5715 patients in the anti-TNF biologic cohort is planned (1:5 accrual ratio). This sample size accrued (uniformly) over a 5-year period and followed by three additional years of follow-up from the time the last patient enrolls (8- year total study duration), will result 90% power at the two-sided 0.05 significance level to detect an increased risk of malignancy (HR of 1.8 or greater). Sample size calculations were calculated using PASS 13.0, The sample size calculation are consistent with the primary endpoint analyses (Section 9.7) and were performed using PASS version 16.0.3 procedure for calculating the sample size for a log-rank test for difference in hazard ratio (consistent with primary endpoint analysis Section 9.7). Inputs of power (.90), alpha (two-sided 0.05), group allocation (0.2:1 for tofacitinib: comparator), hazard rate in the comparator group (.006), and detectable hazard ratio (1.8) were given. An accrual time of 5 years and a total study duration of 8 years was assumed, as was uniform accrual with 10% annual loss to follow-up.

9.6. Data management

For this study, statistical analyses conducted by Corrona and provided to Pfizer will be performed using STATA 15 (StataCorp, LP, College Station, TX). All analyses will be carried out under the direction of the Chief Statistical Officer for Corrona.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Corrona and should not be made available in any form to third parties, except for authorized representatives of Corrona or appropriate regulatory authorities. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic or paper form and will be password-protected, and/or stored in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member, where appropriate, to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents include but are not limited to relevant hospital records or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Corrona agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by Corrona according to local regulations or as specified in the Corrona standard procedures, whichever is longer. Corrona must ensure that the records continue to be stored securely for so long as they are retained.

If Corrona becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Corrona and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

9.7. Data analysis

An overview of the data analyses is given in the sections below. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by Corrona as the sponsor. The SAP may modify the plans outlined here, however any major modifications of primary endpoint definitions or their analyses will be reflected in a protocol amendment.

9.7.1. Patient Demographic and Clinical Characteristics

All patients will be described in terms of demographic characteristics (e.g., age, gender), prior UC therapies received, comorbidities at time of tofacitinib therapy initiation, duration of tofacitinib therapy, disease severity, and subsequent UC treatments received. In addition to the summary of duration of tofacitinib therapy given overall, duration of tofacitinib therapy will also be presented by dose of tofacitinib immediate-release (5mg and 10mg twice daily) and tofacitinib XR (11mg and 22 mg once daily) formulations, along with a summary of usage patterns including the number of patients who change doses.

9.7.2. Analysis for the Primary Objective of Malignancy Incidence

The incidence rate of malignancy excluding NMSC will be calculated in each exposure cohort using the exposure cohort definitions for malignancy given in Section 9.3.1. The analysis of malignancy will include both incident and prevalent users. The unadjusted incidence proportion will be calculated as the number of events per number of patients and presented along with a 95% confidence interval around the proportion. The unadjusted incidence rate will be presented as number of events per 100 person-years, along with a 95% confidence interval around the rate. The primary analysis will be performed in a propsensity score trimmed population (see details below).

To compare the risk of malignancy between the tofacitinib exposure cohort and the anti-TNF biologic cohort and the NMSM cohort, the time to first malignancy event will be analyzed via Cox proportional hazard models. 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 trimming. The proportional hazard assumption will be evaluated. The adjusted hazard ratio from the Cox model will be presented along with a 95% confidence interval around the hazard ratio.

9.7.3. Analysis for the Secondary Objective of NMSC and Non-Malignancy Incidence

The incidence rate of NMSC will be calculated in each exposure cohort using the exposure cohort definitions for malignancy given in Section 9.3.1. The incidence rate of all secondary outcomes will be calculated in each exposure cohort using the exposure cohort definitions for non-malignancy outcomes given in Section 9.3.2. The analysis of non-malignancy, secondary outcomes will include only incident users. Similar to the outcomes for the primary objective, incidence proportions and rates will be presented along with 95% confidence intervals. The primary analysis will be performed in a propensity score trimmed population (see details below). A sensitivity analysis will be performed in a propensity score matched population.

To compare the risk of all secondary malignancy between tofacitinib and anti-TNF biologic therapy and NBSM, the time to first event will be analyzed via Cox proportional hazard models. 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 after propensity score trimming. Time-varying covariates can be included. The proportional hazard assumption will be evaluated. The adjusted hazard ratio from the Cox model will be presented along with a 95% confidence interval around the hazard ratio.

A descriptive analysis examining surgeries for UC occurring among patients treated with tofacitinib or a comparator medication will be completed. Additionally, a descriptive analysis examining physician-reported events will be completed to compare rates of HZ between tofacitinib and comparator cohorts.

9.7.4. Subgroup Analyses of Primary and Secondary Outcomes

There are certain subgroups of patients that are of interest to examine via descriptive or comparative analyses at the time of the final analysis. These include:

- Subgroups based on disease severity
- Subgroups based on dosing of tofacitinib(5mg and 10mg twice daily) and tofacitinib XR (11mg and 22mg once daily) formulations
- Subgroups based on patient age, including subgroup analysis of patients <65 years vs. ≥65years
- Subgroups based on prior treatment group mechanism of action
- Subgroups based on comorbidity status
- Subgroups based on line of therapy (some subgroups may not be applicable)

Because we do not know the sample size in each of these subgroups prior to patient accrual, we will need to calculate power for comparative analyses within subgroups once patient accrual is complete and the sample size for each subgroup is known. At that time, we will evaluate power (assuming observed sample size in the subgroup and patient-years anticipated at the end of the study) for each of the above subgroup analyses and determine whether there is adequate power within the subgroup to justify performing a comparative analysis at the time of the final analysis. The power calculations for this purpose will not use the observed event rate in the tofacitinib cohort, but instead use either the observed event rate in the comparator population, or a published event rate in a population similar to that in the comparator cohort. We define adequate power to perform a comparative analysis within a subgroup of interest is defined as 80% power at the two-sided 0.05 significance level to detect a HR of 2.0 or greater. If we assume a 1:5 allocation of tofacitinib patients to comparator patients, 5 years accrual and 8-year total study duration with 10% annual attrition, and 0.60 malignancy events per 100 patient-years, this would indicate a required sample size for a malignancy comparison of 3673 patients (613 tofacitinib and 3060 comparator patients) within any subgroup. If, for a given subgroup, the sample size does not justify performing a comparative analysis, only descriptive analyses will be performed wherein the crude and age-adjusted rates will be presented along with 95% confidence

intervals for the tofa and comparative cohorts. In that case, no significance testing or additional modeling will be performed within the subgroup.

9.7.5. Propensity Score Methods for Propensity Score Trimming and Matching

As stated above, the primary analysis for the primary and secondary objectives will be performed on propensity score trimmed populations. The steps for determining the trimmed population are as follows:

- Patient demographic and clinical factors at the time of initiation, and prior treatment patterns will be compared between cohorts. Standardized differences and p-values generated from statistical tests comparing the two 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 anti-TNF biologic therapy; propensity for initiating tofacitinib vs. NBSM). 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 initiators and anti-TNF biologic initiators excluding only those patient 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.

- New enrollees to the registry may be either a newly initiating treatment at enrollment or follow-up (incident user) or continuing a treatment prescribed within 12 months of enrollment (prevalent user). Time at risk for new users begins at the start of drug exposure whereas prevalent users have initiated therapy up to 12 months prior to enrollment. Consequently, prevalent users may have greater drug tolerability and may be less likely to experience an adverse event during registry follow-up than incident users. Including prevalent users in the malignancy analyses has the potential to bias the estimates towards the null. Adjusting for baseline confounders is also more complicated as the baseline time is different for new and continuing users. To address these issues, separate propensity score models will be considered for incident and prevalent users in the primary analysis, and an indicator for incident versus prevalent use can be included in the outcome models. Propensity score matching will also be considered separately between the groups. The analyses of secondary outcomes will use only new users unless the number of patients available for analysis is prohibitively small. An alternative approach, which will be considered a sensitivity analysis, is to use the propensity score to match tofacitinib initiations to biologic initiations (and tofacitinib initiations to NBSM initiations). One-to-many matching

can be carried out with a low caliper (maximum difference allowed), generally set to 0.01. The anti-TNF biologic initiation sample at the time of the analysis will inform the caliper – larger sample sizes allow for stricter matching without loss of sample size.

Reporting associated with final analyses of the primary malignancy endpoint will include case summary table(s) summarizing patient and case details for physician-reported malignancy events included in the study, for which insufficient medical records were available to support adjudication at the time of the final data lock.

9.7.6. Analyses for the Interim, Comparative Safety Report

An interim, descriptive comparative safety report will be produced after all patients have accrued (Section 6) to support Pfizer's ongoing safety monitoring activities. However, no comparative analyses (i.e. no statistical tests) will be performed in any of these reports. Although this report has been called an "interim" report, this will not present results of an interim comparative analysis. The comparative analyses described above for both primary and secondary endpoints will only be performed at the time of the final analysis (when all patients have accrued and when the planned follow-up time has been completed). The interim, descriptive comparative safety reports will provide rates of targeted adverse events observed in the study population by groups covering the time from first reported tofacitinib use to the data cut date. The report will provide cumulative incidence rates in each cohort from index date to the data cut date used for the report.

9.8. Quality control

This study will use data collected as part of the Corrona IBD Registry. Sites that contribute to the Corrona IBD Registry are subject to periodic onsite and remote monitoring visits by Corrona monitors to ensure that the Corrona registry protocol, data collection requirements and applicable research regulations are being followed. The monitors may review source documents (i.e. original medical records) to confirm that the data recorded on questionnaires and CRFs are accurate (except for pre-identified source data directly recorded on the questionnaires or CRF). The Investigator and institution will allow Corrona monitors and appropriate regulatory authorities to have direct access to source documents to perform this verification. These personnel, bound by patient privacy laws, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

The study site may also be subject to review by the IRB, and/or to quality assurance audits performed by Corrona, or companies working with or on behalf of Corrona, and/or to inspection by appropriate regulatory authorities.

9.9. Strength and Limitations of the Research Methods

This observational study is designed to assess the safety of tofacitinib among UC patients within the real-world clinical practice setting utilizing the Corrona IBD registry, a recently established US-based IBD registry. Data for the registry are systematically collected from patients and physicians and are independently analyzed by Corrona statisticians and

epidemiologists. Exposure, outcome, and covariate information is collected by physician and patient reports. Supporting documentation is requested for all TAEs to support validation activities, thereby limiting the possibility of information bias. In addition to robust data collection, this study uses multiple methodologies, including propensity scores, to assess association of safety endpoints.

Despite the strengths of the registry, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification, and generalizability are of concern when evaluating event rates.

As a new therapy in the UC treatment armamentarium, it is possible that patients treated with tofacitinib 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 adverse events. Biases resulting from channeling may present as increased rates of adverse events in the early phases of the study. Comparison to internal comparators may illuminate such channeling. Stratification on key indicators of disease severity, patient characteristics and past therapies can be done for contextualization. Trend analyses may be conducted to evaluate rates over time.

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While the Corrona registry has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, a hybrid reporting system has been adopted to utilize the fullest extent of data available. As highlighted previously (Section 9.3.1), primary analyses will include all validated endpoints via a combination of physician report on Provider Follow-up or Exit Questionnaires and follow-up TAE forms (completed by the physician). Secondary analyses will include reports by physician report only, as well as fully adjudicated endpoints using available source documentation. Doing so will provide a range by which to estimate event reporting rates in the study population.

Additionally, the Corrona IBD Registry enrolls patients who have initiated a FDA-approved treatment. As a result, new enrollees to the registry may be either a new (incident) user or continuing (prevalent) user. Time at risk for new users begins at the start of drug exposure whereas prevalent users are a select group of patients who have initiated therapy prior to enrollment. Consequently, prevalent users may have greater drug tolerability and may be less likely to experience an adverse event than new users. Including prevalent users in analyses has the potential to bias the estimates towards the null. Adjusting for baseline confounders is also more complicated as the baseline time is different for new and continuing users. To address these issues, separate propensity score models will be estimated for new and continuing users in the primary analysis. Propensity score matching will also happen separately between the groups. The analyses of secondary outcomes will use only new users unless the number of patients available for analysis is prohibitively small.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form, depending on site capabilities, and will be password protected (electronic records) or secured in a locked room (paper-based records) to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by the Corrona IBD Registry. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, registry and patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

This study uses data that are routinely collected as part of the Corrona IBD Registry. Informed consent is a part of the existing registry process, and as such only data from patients who have consented to participate in the registry will be used in this study. For all data collected as part of the Corrona IBD Registry the informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The Corrona IBD Registry requires that investigators participating in the registry ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation in the Corrona IBD Registry, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data. Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the

patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, obtains written informed consent (unless verbal assent is obtained as described above) from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator retains the original of each signed consent form.

10.3. Patient withdrawal

Patients may withdraw from the Corrona IBD Registry at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the registry, and also withdraws consent for disclosure of future information, no further evaluations are performed, and no additional data are collected.

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

The Corrona IBD Registry protocol was initially approved by the IntegReview IRB on 24 March 2017. Approval was renewed on 13 March 2018.

Investigator sites that contribute to the registry are responsible for obtaining approval to participate in the registry study by the designated Central IRB, or through local or academic IRBs (where institutionally required).

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 by the investigator. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the FDA Guidance for Industry, Good Pharmacovigilance and Pharmacoepidemiologic Assessment. Per Pfizer's subscription to the Corrona database, analyses may be conducted by authorized third parties and in accordance with Corrona scientific review policies.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

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

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios (or special situation reports) involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these adverse events with an explicit attribution or scenarios (or special situation reports) involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

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

- "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)*"

- "*Your Reporting Responsibilities: Supplemental Training for Vendors Working on Pfizer Studies*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

An interim report and a final report, reflecting data for the 8 year study period, will be submitted to Pfizer and the US FDA communicating the full study experience. Additionally, this study will be posted on the European Union (EU) Post-Authorisation Study (PAS) register. Some or all of the data from this study may be developed into abstracts for presentation at scientific conferences, and/or developed into manuscripts for external publication purposes.

Corrona will immediately report (within 1 business day) to Pfizer any urgent safety measures taken to protect the study patients against any immediate hazard, and or any serious breaches of this NI study protocol that Corrona becomes aware of.

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.

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14. LIST OF TABLES

15. LIST OF FIGURES

16. APPENDIX 1 - MINIMUM SUPPORTING DOCUMENTATION REQUIREMENTS BY TARGETED EVENT TYPE

Event Type	Admission Summary	Discharge Summary[1]	Procedure Summary, Operative Report	Laboratory Data	Biopsy/Pathology Report	Imaging Studies	Specialist consultation summary	Cultures , PCR Results	Electrocardiogram (ECG)	Cardiovascular Studies (ECHO, Stress test, etc.)	Medication Administration Record	Chemotherapy and/or Radiation Records	Critical Care Flow sheet	Emergency Dept. Record/Summary	Death Certificate[2]	Death Summary (hospital or ambulance reports, etc.)[2]	Autopsy Report[2]
Cancer/Malignancy	•	◑	•	•	◑	•	❩				•	•			◑	◑	◑
Serious Infection[3]	•	◑	•	•	•	•	•	❩	•		◑		•	•	To be submitted for any events resulting in death, whenever possible.		
Cardiovascular	•	◑	❩	❩		•	❩		❩	•	•		•	•			
Hepatic	•	◑	•	•	❩	•	•										
Autoimmune	•	◑		•	•	•	❩		•	•	•						
Neurologic	•	◑	•			❩	❩							•			
Anaphylaxis/severe hypersensitivity reaction	❩	◑					•				◑		❩	❩			
General Serious	❩	◑	•	•	•	•	•	•	•	•	•		•	•			
Pregnancy	❩	◑	•	•			•				•		•	•			

◑ Required records[4] , where applicable

❩ Expected/important records (site should attempt to obtain)

• Please provide records if available, as applicable

[1] Admission and discharge summaries should be provided to support any inpatient hospitalizations, whenever possible.

[2] Cases resulting in death should include death summary, death certificate, autopsy reports and any hospital records or procedure reports supporting the circumstances around the outcome, whenever possible.

[3] Hospital discharge summary and records to support treatment with intravenous or intramuscular antibiotics (as applicable) should be provided for serious infection events requiring hospitalization. Treatment records are *required* for cases of serious infections treated in the outpatient setting.

[4] As applicable, sites should exercise due diligence in attempts to obtain critical records for serious events involving hospitalization.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Not applicable	14-Sep-2018	IBD-600 Corrona IBD Registry Protocol
2	Not applicable	14-Sep-2018	IBD-600 Corrona IBD Registry Questionnaires
3	Not applicable	TBD	Pfizer A3921329 Protocol - Draft tables: summary statistics for endpoints of interest
4	Not applicable	TBD	Letter of Administrative Change: Corrona-IBD-600 protocol (dated 02 JAN 2019, updates to eligibility requirements)

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required

ANNEX 3. ADDITIONAL INFORMATION

Not applicable