NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Active Surveillance, Post-Authorization Study to Characterize the Safety of Tofacitinib in Patients With Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data From the United Registries for Clinical Assessment and Research (UR-CARE) in the European Union (EU)
Protocol number	A3921352
Protocol version identifier	4.0
Date	27 February 2023
EU Post Authorization Study (PAS) register number	Pending (prior to start of data collection)
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-014
Procedure number	EMEA/H/C/004214/X/0005/G
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No

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

	biologics and immunosuppressants (comparator cohorts as described below). 2. Estimate the incidence rates of primary and secondary safety events of interest stratified by tofacitinib dose (5 mg vs. 10 mg dose). 3. Estimate the hazard ratios of the primary and secondary safety events of interest between tofacitinib-treated patients (Cohort 1) and comparator Cohorts 2, 3 and 4 described below, assuming sufficient statistical power. <u>Tofacitinib cohort</u> Cohort 1: UC patients initiating tofacitinib, stratified by prior biologic use (i.e., patients naïve to biologic vs. patients with prior biologic use who initiate tofacitinib) Cohort 2: UC patients who initiate biologics, with/without concurrent immunosuppressants, stratified on tumor necrosis factor inhibitor (TNFi)/non-TNFi use and number of previous biologic treatments Cohort 3: UC patients who initiate immunosuppressants without concurrent biologics Cohort 4: UC patients naïve to both biologics and immunosuppressants
Countries of study	Multiple European Union (EU) nations including France, Belgium, Bulgaria, Spain, The Netherlands and other EU countries as sites start using UR-CARE
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADD	Average daily dose
AE	Adverse event
AEM	Adverse event monitoring
AZA	Azathioprine
BID	Bis in die (Twice a day)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
DALY	Disability adjusted life years
DDD	Daily defined dose
DVT	Deep vein thrombosis
ECCO	European Crohn's and Colitis Organization
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EU	European Union
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HZ	Herpes zoster
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICF	Informed consent form
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JAK	Janus kinase
MACE	Major adverse cardiac events
MI	Myocardial Infarction
MTX	Methotrexate
NI	Non-interventional
NMSC	Non-melanoma skin cancer
NSAIDs	Non-steroidal anti-inflammatory drugs
PASS	Post-Authorization Safety Study
PE	Pulmonary embolism
PML	Progressive multifocal leukoencephalopathy
PY	Person-years

Abbreviation	Definition
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SPSS	Statistical Package for the Social Sciences
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
UR-CARE	United Registries for Clinical Assessment and Research
vs	Versus
VTE	Venous thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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Country Coordinating Investigators

Not applicable

4. ABSTRACT

- **Title**: An Active Surveillance, Post-Authorization Study to Characterize the Safety of Tofacitinib in Patients With Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data From the United Registries for Clinical Assessment and Research (UR-CARE) in the European Union (EU)

- **Main authors/affiliation**: Yamile Zabana, MD, PhD, GETECU; Manuel Barreiro, MD, PhD, GETECU; Nana Koram, PhD, MPH, Pfizer, Inc.

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

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

- **Objectives**: The primary objective is to estimate the incidence rates of malignancy excluding NMSC, and incidence rates of VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]) (primary safety events) in adult UC patients who initiate tofacitinib in the course of routine clinical care (Cohort 1 as described below), as well as the incidence rates in UC patients treated with other approved systemic agents such as biologics and immunosuppressants, and in UC patients naïve to biologics and immunosuppressants (comparator cohorts as described below).

  There are 3 secondary objectives:

  1. Estimate the incidence rates of other safety events of interest including (but not limited to) NMSC, lung cancer, lymphoma (overall and by three main subtypes: Hodgkin's lymphoma, non-Hodgkin's lymphoma, and chronic lymphocytic lymphoma), opportunistic infections (e.g., tuberculosis), major adverse cardiac events (MACE), myocardial infarction (MI), serious infections defined as infections requiring hospitalization, herpes zoster (HZ), progressive multifocal

leukoencephalopathy (PML), gastrointestinal (GI) perforations, fractures, and all-cause mortality (secondary safety events) in adult UC patients who initiate tofacitinib in the course of routine clinical care (Cohort 1 as described below), as well as the incidence rates in UC patients initiating treatment with other approved systemic agents such as biologics and immunomodulators/immunosuppressants, and in UC patients naïve to biologics and immunomodulators/immunosuppressants (comparator cohorts as described below).

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

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

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

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

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

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

Patients in Cohorts 2, 3 and 4 are expected to have less severe disease compared with tofacitinib-treated patients, since, as per the EU summary of product characteristics (SmPC), patients prescribed tofacitinib are expected to have failed biologics or conventional therapy prior to tofacitinib prescription. Thus, patients in Cohorts 2, 3 and 4 may not be adequate comparator cohorts.

- **Study design**: This is an active cohort study of adult UC patients aged ≥18 years treated with tofacitinib compared to patient receiving alternative treatment or not treatment. The study will use secondary data collected in the UR-CARE platform, which is an ongoing, prospective, observational, cohort of European Union (EU) patients with inflammatory bowel disease (IBD) with the primary aim of facilitating daily patient care and research

studies in IBD. This study will focus only on UC patients enrolled in the UR-CARE platform.

- **Population**: The study population will include adult UC patients aged ≥18 years enrolled in UR-CARE who are initiating treatment with tofacitinib (Cohort 1) from 01 July 2018 (date of approval of tofacitinib for UC patients in the EU) through 31 March 2025. The study will also include the following comparator cohorts: Cohort 2: UC patients who initiate biologics, with/without concurrent immunomodulators/immunosuppressants, stratified on TNFi/non-TNFi use and number of previous biologic treatments; Cohort 3: UC patients who initiate immunomodulators/immunosuppressants without concurrent biologics; Cohort 4: UC patients naïve to both biologics and immunomodulators/immunosuppressants.

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

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

- **Data sources**: Baseline and follow-up data, including patient demographics, disease characteristics, and treatment will be based on data from the UR-CARE platform. Data are entered into the UR-CARE platform in two ways: via direct data entry by treating physicians, and also via data linkage from joining national IBD registries.

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

Preliminary power calculations assume a 0% annual rate of switching, a fixed power of 80% at α=0.05, an estimated 2386 IBD patients on TNFi, estimated rate in patients of 5.39/1000

person-years (PY) for malignancy, and estimated rate of VTE in IBD patients of 2.4/1000 PY based on published literature (estimates based on data available in published literature from UR-CARE participating countries), 7-year total study duration (6 years of patient accrual, and a minimum of 12 months follow-up for the last enrolled patient), and a 5% annual loss to follow-up in both cohorts.

For an event with a rate of 5.39/1000 PY, such as malignancy, sample sizes of 500 to 1000 tofacitinib-treated patients would allow for minimum relative risks of 2.2 and 1.9, respectively, to be detected between the tofacitinib and TNFi/non-TNFi cohorts.

For an event with a rate of 2.4/1000 PY, such as VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for minimum relative risks of 3.1 and 2.4, respectively, to be detected between the cohorts.

Assuming a 30% annual rate of switching, the detectable relative risks between the tofacitinib and TNFi/non-TNFi cohorts at 80% power and $\alpha = 0.05$ are higher (i.e., for malignancy), sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 7.2 and 5.1, respectively, while for VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 13.3 and 8.7, respectively.

Based on these estimations, comparative analyses will be performed if there are ≥500 patients in the tofacitinib cohort, which would allow for between 2.2 to 13.3 relative risk to be detected with 80% power at the 5% significance level, assuming 0% to 30% annual switching between the tofacitinib and biologic cohorts.

- **Data analysis:** This study will include descriptive summaries of baseline characteristics of the tofacitinib cohort (Cohort 1), biologics cohort (Cohort 2), immunomodulators/immunosuppressants cohort (Cohort 3) and naïve cohort (Cohort 4).

Crude incidence rates (with corresponding 95% confidence intervals) of the safety events of interest as specified in the primary and secondary objectives will be estimated for each cohort.

If the study size assumptions listed above are met, incidence rates of the primary and secondary safety events of interest will be compared between the tofacitinib cohort and Cohorts 2, 3 and 4 using propensity score matched multivariable Cox regressions to obtain hazard ratios adjusted for sex, age, year of treatment start, disease severity, comorbidities and other potential confounders for more refined evaluation of safety endpoints.

Several sub-group analyses will also be conducted. Incidence rates of the primary and secondary safety events of interest will be stratified by:

- prior biologic use (prior biologic use vs. none; among those with prior biologic use, 1st biologic vs. 2nd biologic vs. ≥3 biologic);
- patient age (patients aged ≥50 years vs. <50 years;

- patients aged ≥65 years vs. <65 years);
- tofacitinib dose;
- patients with ≥1 VTE risk factors vs. no VTE risk factors (for the outcomes of VTE and MACE), and smoking status (for the outcomes of malignancy, excluding NMSC, lung cancer, MACE and MI).

If the assumptions listed above are met, comparative assessments between the tofacitinib cohort and comparator cohorts will be conducted, otherwise crude and age-adjusted rates will be presented along with 95% confidence intervals for all 4 cohorts.

- **Milestones**:

  Start of data collection: 31 January 2024
  Interim report: 31 August 2024
  End of data collection: 31 March 2026
  Registration in the EU PAS register: Pending (prior to start of data collection)
  Final study report: 31 March 2027

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0	November 2021	Title Page	Updated protocol identifier (version) and date. Updated secondary objective to include capture of lymphoma subtypes.	Editorial change. PRAC request.
	November 2021	Section 4	Revised Abstract to align with revisions in other sections of the protocol. Revised milestone for start date of data extraction to begin after expected protocol endorsement by PRAC/CHMP.	PRAC request. To align with expected procedural completion.
	November 2021	Section 6	Revised milestone for start date of data extraction to begin after expected protocol endorsement by PRAC/CHMP.	To align with expect procedural completion.
	November 2021	Section 8	Deleted last paragraph	PRAC request.
	November 2021	Section 9.1	Revised study design description.	PRAC request and clarification.
	November 2021	Section 9.2	Updated list of participating countries and included the country's corresponding effective reimbursement date. Deleted description of data entry and moved to Section 9.4.1.	PRAC request and clarification. PRAC Request.
	November 2021	Section 9.2.1.1	Revised inclusion criteria for Cohort 1.	PRAC request and clarification.
	November 2021	Section 9.2.1.2	Revised inclusion criteria for Cohort 2.	PRAC request and clarification.
	November 2021	Section 9.2.1.3	Revised inclusion criteria for Cohort 3.	PRAC request and clarification.
	November 2021	Section 9.2.1.4	Revised inclusion criteria for Cohort 4.	PRAC request and clarification.
	November 2021	Section 9.3.1.1	Added 'Inpatient care because of UC' to list of VTE risk factors.	PRAC request.
	November 2021	Section 9.3.2	Updated information on data captured to define exposure.	PRAC request and clarification.
	November 2021	Section 9.3.6	Added 3 main lymphoma subtypes to Secondary endpoints.	PRAC request.

	November 2021	Section 9.4.1	Added launch date of UR-CARE Added information on number of IBD patients in UR-CARE platform. Added information on National Study Groups. Moved information on data entry from Section 9.2. Added Figure 1 to describe data processing.	PRAC request. PRAC request. PRAC request. PRAC request. PRAC request.
	November 2021	Section 9.5	Updated to refer to biologic cohort instead of TNFi only comparator.	PRAC request and clarification.
	November 2021	Section 9.8	Updated description quality control procedures to clarify procedures to ensure consistency, accuracy, and completeness of collected data.	PRAC request and clarification.
	November 2021	Section 9.9	Updated discussion on capture of VTE risk factors. Updated discussion on potential differences in missingness of data collected retrospectively versus prospectively.	PRAC request. Provide clarification.
	November 2021	Appendix 1	Added Appendix with MedDRA coding for safety endpoints.	PRAC Request.
	November 2021	Annex 2	Updated signature date.	Editorial change.
2.0	May 2022	Abstract	Updated data sources section to indicate the two ways that data are entered on the UR-CARE platform Updated milestone dates section to reflect new timelines Other minor editorial changes throughout	PRAC request and clarification Editorial changes
		Section 6	Milestone dates updated	Editorial change
		Section 9.2.1.2	Updated to include list of specific biologics to be evaluated during study	PRAC request and clarification
		Section 9.2.1.3	Updated to include list of specific immunosuppressants to be evaluated during study	PRAC request and clarification
		Section 9.2.1.4	Updated to include examples of medications that patients in Cohort 4 may be receiving	PRAC request and clarification

		Section 9.2.2	Exclusion criteria updated to note that UC patients on drugs not approved for UC will be excluded unless the medication later becomes approved for UC during the course of the study prior to the data cut off points for the interim and/or final study reports; also updated to note that patients on other JAKi will be excluded as focus of study is on tofacitinib	Clarification
		Section 9.3.1.1	Updated to note that the variable "Inpatient care because of UC" will be assessed from date of hospital admission to date after patient discharge	PRAC request and clarification
		Section 9.3.2	Exposure variables updated to specify list of biologics and list of immunomodulators/immunosuppressants to be assessed during study	PRAC request and clarification
		Section 9.4.1	Several subsections added to further describe existing national IBD databases that have adopted UR-CARE	PRAC request and clarification
		Section 9.4.2	Added new section and subsections to describe the two ways of entering data on the UR-CARE platform, including addition of Figure 2 to illustrate process of data linkage	PRAC request and clarification
		Section 9.7.5	Editorial changes	Editorial changes
		Section 9.7.7	Updated to note that "A comparison of patient baseline characteristics, drug exposure and safety endpoints of interest will also be conducted between similar cohorts for the different data sources used by UR-CARE (ie, data as entered directly by HCPs through the UR-CARE platform will be compared with data as linked from each of the joining national IBD registries)." Updated to reflect single interim report	PRAC request and clarification Editorial change
		Section 9.7.8	Updated to note that "A comparison of patient baseline characteristics, drug exposure and safety endpoints of interest will also be conducted between similar cohorts for the different data sources used by UR-CARE (ie, data as entered directly by HCPs through the UR-CARE platform will be compared with data as linked from each of the joining national IBD registries)."	PRAC request and clarification

			Also updated to note that "Data from each of the joining national IBD registries will be evaluated for completeness in regard to essential data elements (ie, drug exposure and safety endpoints) for this PASS, and additional sensitivity analyses will be conducted excluding data from low-quality sources during the final analyses (descriptive, comparative analyses, and stratifications)."	
		Section 9.9	Updated to describe limitations associated with national IBD databases joining the UR-CARE platform	PRAC request and clarification
		Section 12	Other minor editorial changes	Editorial change
		Section 13	Updated to include additional references	Editorial changes
		Appendix 14.2	New appendix added to provide a table showing overview of essential data elements as captured by direct entry and as captured with joining national IBD registries using ENEIDA as an example	PRAC request and clarification
		Section 16	Updated to include figure 2	PRAC request and clarification
		Annex 2	Updated signature date	Editorial change
3	February 2023	Abstract	Updated planned start of data collection to 31 January 2024. This date represents the date of data extraction to begin analysis for the interim report. Patient accrual is not impacted as study is secondary data collection	Editorial change
		Section 6	Updated planned start of data collection to 31 January 2024. Footnote added to explain that this date represents the date of data extraction to begin analysis for the interim report. Patient accrual is not impacted as study is secondary data collection	Editorial change
		Section 9.2.1.2	Correction of typo to inclusion criteria to specify biologic agent	Editorial change (typo correction)
		Section 9.2.1.3	Correction of typo to inclusion criteria to specify immunosuppressive agent	Editorial change (typo correction)
		Section 9.2.1.4	Correction of typo to inclusion criteria to delete reference to tofacitinib	Editorial change (typo correction)

		Annex 2	Updated signature date	Editorial change

6. MILESTONES

Milestone	Planned date
Start of data collection*	31 January 2024
End of data collection	31 March 2026
Interim report **	31 August 2024
Registration in the EU PAS register	Pending (prior to start of data collection)
Final study report***	31 March 2027

*Represents date of data extraction for start of data analysis for interim report. Patient accrual is not impacted as study is secondary data collection
** Anticipated to include data 01 July 2018 - 30 December 2023
*** Anticipated to include data 01 July 2018 - 30 March 2026

7. RATIONALE AND BACKGROUND

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

Regarding the prevalence of UC, estimates for European populations vary widely, from 2.4 per 100,000 persons in Romania to 505 per 100,000 persons in Norway[3]. The EMA's Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (Committee for Medicinal Products for Human Use [CHMP]/Efficacy Working Party [EWP]/18463/2006 Revision 1), estimates prevalence to be 70 to 500 cases per 100,000 with peak age of onset between 15 and 25 years. In 15% of cases, UC is diagnosed in childhood and may present before school age[5]. Data from multiple countries suggest increasing prevalence over time[3,6].

UC presents significant health and socioeconomic burdens for the individual patient and society[7,8,9]. There is currently no cure for UC[1]. Moderate-to-severe UC often requires treatment with systemic agents, such as glucocorticoids and azathioprine[10], many of which

are associated with infectious, cardiovascular, gastrointestinal and malignant adverse events[11,12]. Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the European Union (EU) in July 2018 at a dose of 5 mg twice daily (BID) or 10 mg BID for the treatment of adults with moderate-to-severe UC, who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Malignancy excluding NMSC is an important potential risk associated with the use of tofacitinib. In January 2020, as a result of a reassessment of the benefit-risk of tofacitinib, the European Commission (EC) approved several revisions to the Summary of Product Characteristics (SmPC), including addition of VTE as an important identified risk associated with the use of tofacitinib.

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

Active surveillance studies can estimate incidence rates of safety events of interest overall and within strata of disease severity, treatment history, and other concomitant therapy. The goal of this active surveillance study using data from the United Registries for Clinical Assessment and Research (UR-CARE platform) is to assess the risk of malignancy excluding NMSC, VTE, and other safety events of interest in UC patients initiating treatment with tofacitinib in a realworld setting. Incidence rates of the same endpoints will be estimated for adult UC patients treated with other approved systemic medications, as well as adult UC patients naïve to both biologics and immunomodulators/immunosuppressants, to provide context to the findings.

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

8. RESEARCH QUESTION AND OBJECTIVES

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

Primary Objective:
The primary objective is to estimate the incidence rates of malignancy, excluding NMSC and incidence rates of VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]) among adult UC patients aged ≥18 years who initiate tofacitinib in the course of routine clinical care (Cohort 1), as well as the incidence rates in UC patients treated with other

approved systemic agents such as biologics and immunosuppressants, and in UC patients naïve to biologics and immunosuppressants (comparator cohorts).

Secondary Objectives:

There are 3 secondary objectives:

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

- NMSC
- Lung cancer
- Lymphoma (including 3 main subtypes Hodgkin's lymphoma, non-Hodgkin's lymphoma, and chronic lymphocytic lymphoma)
- Serious infections
- Opportunistic infections (e.g., tuberculosis)
- Herpes zoster (HZ)
- Major adverse cardiac events (MACE)
- Myocardial infarction (MI)
- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Fractures
- All-cause mortality

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

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

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

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

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

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

9. RESEARCH METHODS

9.1. Study design

This is a 7-year active cohort study of adult UC patients aged ≥18 years treated with tofacitinib compared to patients receiving alternative treatment or no treatment. The study will use secondary data collected in the UR-CARE platform. To allow for a minimum follow-up duration of 12 months, UC patients meeting the study entry criteria through 31 March 2025 will be included in the analysis, follow-up of patients for the study will end 31 March 2026.Incidence rates and associated 95% confidence intervals (CIs) of the safety events of interest will be calculated in all 4 cohorts. Data capture and follow-up methods are the same for all 4 cohorts within the UR-CARE platform. For both primary and secondary safety events of interest, comparative analyses will be conducted as described in Section 9.7.

9.2. Setting

The UR-CARE platform is set up for daily care use (i.e. individual sites may upload patient information directly onto the UR-CARE platform) and contains medical records, including identifying data, of patients from multiple EU and non-EU countries. The following is a list of participating countries with their effective reimbursement date for tofacitinib:

- France (June 2019)
- Belgium (September 2019)
- Bulgaria (May 2019)
- Spain (September 2019)
- The Netherlands (September 2018)
- Greece (January 2021)
- Poland (September 2020)
- Slovenia (June 2019)
- Croatia (April 2019)
- Romania (October 2021)
- United Kingdom (February 2019)

Updates on information related to patient enrolment from the participating countries as well as inclusion of new sites or study groups will be provided in the interim report.

In addition, a prospective study requires patients to sign a separate ICF to allow the treating physician to access the study module and capture study specific data such as safety events. The prospective module data become accessible only after the physician has confirmed that patients have signed the study specific ICF. Data from all patients will be entered on the UR-CARE platform, but to protect patients' confidentiality, only anonymized data from those who have accepted to participate in the study will be provided on the research platform for analysis by the research team.

This PASS will be conducted on behalf of the Sponsor by B-COM, a contract research organization based in France.

9.2.1. Inclusion criteria

The active surveillance population includes adult UC patients aged ≥18 years enrolled in the UR-CARE platform who are newly treated with tofacitinib following EMA approval in July 2018 through 31 March 2025. The study will also include 3 comparator UC cohorts as defined below. Patients in all 4 cohorts must have a minimum of 12 months of medical history available either in UR-CARE (data source described in Section 9.4) prior to the index date (as defined in Section 9.3.3 to allow for adequate capture of baseline variables (Section 9.3.1). Additionally, a minimum follow-up duration of 12 months will allow evaluation of safety events of interest.

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

1. Initiation of tofacitinib (i.e., first ever prescription) as captured in the UR-CARE platform from 01 July 2018 through to 31 March 2025.

2. Patients with UC diagnosis per ECCO guidelines as established by the treating physician" will be eligible for inclusion. The severity of the disease will be confirmed with clinical parameters (such as ulcerative colitis disease activity index [UCDAI] or Mayo score) as provided in patient medical records.

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

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

simultaneous use of tofacitinib and a biologic concomitantly, should it occur, will be assigned to the tofacitinib cohort.

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

1. Initiation (i.e., first prescription) of a specific biologic agent (any TNFi [adalimumab and biosimilars, infliximab and biosimilars, and golimumab] or non-TNFi agent [vedolizumab and ustekinumab]) as captured in the UR-CARE platform from 01 July 2018 through to 31 March 2025

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

3. Patients with UC diagnosis per ECCO guidelines as established by the treating physician" will be eligible for inclusion. The severity of the disease can be confirmed with clinical parameters (such as UCDAI or Mayo score) as provided in patient medical records.

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

Patients in this cohort may also be on immunosuppressants concurrently.

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

1. Initiation (i.e., first prescription) of a specific immunosuppressant agent (azathioprine, 6-mercaptopurine, methotrexate, tacrolimus, cyclosporine,) (without concurrent biologic therapy) as captured in the UR-CARE platform from 01 July 2018 through to 31 March 2025.

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

3. Patients with UC diagnosis per ECCO guidelines as established by the treating physician" will be eligible for inclusion. The severity of the disease will be confirmed with clinical parameters (such as UCDAI or Mayo score) as provided in medical records.

4. Patients must not have any records of Crohn's Disease (CD) or IBD unspecified (IBD-U) in UR-CARE between the last UC diagnosis and index date [ie, date of first prescription for specific immunosuppressant agent]

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

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

2. Patients with UC diagnosis per ECCO guidelines as established by the treating physician" will be eligible for inclusion. The severity of the disease can be confirmed with clinical parameters (such as UCDAI or Mayo score) as provided in patient medical records.

3. Patients diagnosed with UC since 01 July 2018 through to 31 March 2025.

4. Patients with no history of surgery for UC (surgery suggests more severe disease, and such patients would not be representative of patients with generally mild disease in Cohort 4).

5. Patients must not have any records of Crohn's Disease (CD) or IBD unspecified (IBD-U) in UR-CARE between the last UC diagnosis and index date.

Patients in this cohort (i.e., Cohort 4) can include patients who are steroid-naïve (e.g., patients treated only with aminosalicyclates, balsalazide, mesalazine , olsalazine, and sulfasalazine), patients who are steroid responsive (i.e., patients who receive intermittent courses of steroids), as well as patients not receiving any prescribed medications for the treatment of their disease.

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

9.2.2. Exclusion criteria

Patients not meeting the inclusion criteria for any of the respective cohorts, or patients refusing to sign the Informed Consent Form to authorize utilization of their data will be excluded. Additionally, UC patients captured on the UR-CARE platform may also be prescribed other biologics or immunosuppressants/immunomodulators not yet approved for the treatment of UC in the EU and thus not listed above. Such patients will be excluded from the analysis for this study unless the medication later becomes approved for UC during the course of the study prior to the data cut off points for the interim and/or final study reports. Note that as the focus of this study is on tofacitinib, all other JAK inhibitors will be excluded from analysis for this PASS.

9.3. Variables

9.3.1. Baseline Variables

Physicians enter data from patient medical records to identify non-demographic baseline variables. The baseline period for all cohorts will be the 12 months prior to index date (as defined in Section 9.3.3). Baseline data considered include, but are not restricted to, the following: age, sex, age of UC onset/years since diagnosis, comorbidities within 12 months of the index date for non-malignancy events (e.g., history of serious infection, history of opportunistic infection, history of herpes zoster, history of VTE, history of diabetes mellitus, history of myocardial infarction [MI], history of hypertension), and ever for malignancy events (i.e., history of malignancies), use of immunosuppressants or biologics at index date, and use of immunosuppressants or biologics prior to the index date. Use of the following medications 12 months prior to the index date will also be captured: hormonal therapy and contraceptives, oral steroids, oral nonsteroidal anti-inflammatory drugs [NSAIDs], antimicrobials, anticoagulants, beta blockers, bisphosphonates, narcotics, proton pump inhibitors [PPIs] and statins.

9.3.1.1. VTE risk factors

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

- Age
- Smoking status
- Previous VTE
- Undergoing major surgery from date of hospital admission to 1 month after date of discharge
- MI within previous 3 months prior to index date (defined in Section 9.3.3)
- Heart failure
- Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date
- Malignancy
- Diabetes
- Hypertension
- Inherited coagulation disorders
- Inpatient care because of UC from date of hospital admission to date after patient discharge
- Immobilization
- Obesity

9.3.2. Exposure variables

Exposure to tofacitinib, biologics (specifically adalimumab and biosimilars, infliximab and biosimilars, golimumab, vedolizumab and ustekinumab), and

immunosuppressants/immunomodulators (specifically azathioprine, 6-Mercaptopurine [6-MP], methotrexate, tacrolimus, and cyclosporine) are captured from patient medical records provided by the UR-CARE sites and uploaded onto the UR-CARE platform. Specifically, information on induction start date of prescription, dose, and frequency will be collected, as well as information on maintenance treatment, including start date, dose, frequency, treatment status, stop date, and reason for stopping.

9.3.2.1. Duration of exposure

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

9.3.2.2. Tofacitinib dose calculation

As per the current SmPC, tofacitinib use in UC patients consists of an induction and maintenance phase, with dosage varying depending on phase. During induction treatment, the recommended dose is 10 mg BID for 8 weeks and then 5 mg BID for maintenance. However, the induction dose of 10 mg BID may be extended for an additional 8 weeks if an adequate therapeutic benefit has not been achieved (16 weeks total), followed by 5 mg BID for maintenance. For patients who have failed at least 1 biologic therapy and lost response to 5 mg BID, 10 mg BID can be considered for maintenance therapy, although this treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available.

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

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

Time period 1: Induction period

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

Time period 2: Mixed induction/maintenance period

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

As per the SmPC, maintenance can begin at either the end of Week 8 or at the end of Week 16 so this time period will be a mix of induction and maintenance, and it would not be possible to distinguish between the 2 treatment phases in UR-CARE.

Time period 3: Maintenance period

- ≥ Week 17 (≥ Day 113)

Additionally, average daily dose (ADD) will be estimated using daily defined dose (DDD).

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

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

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

9.3.3. Index date

Index date will be defined as follows:

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

Cohort 2: This will be the date of first prescription for a specific biologic agent since 01 July 2018, following diagnosis of UC as described in Section 9.2.1.2. For patients with more than 1 biologic initiation, more than 1 index date will be defined (e.g., 1 for each biologic initiation).

Cohort 3: This will be the date of first prescription for a specific immunomodulator/immunosuppressant agent since 01 July 2018, following diagnosis of UC as described in Section 9.2.1.3. For patients with more than 1 immunomodulator/immunosuppressant initiation, more than 1 index date will be defined.

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

9.3.4. Follow-Up

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

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

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

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

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

9.3.5. Medication restarts

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

However, treatment episodes that include medication restarts will affect the analysis of non-malignancy events such as serious infections. Patients restarting medications may have a different risk for study endpoints relative to patients who initiate or continue treatment. Therefore, patient characteristics and incidence rates of safety events will be compared for

those who restart medications and those who do not, to determine if it is appropriate to include both types of patients in the same analysis. If no significant difference exists between these groups, all treatment episodes will be analyzed together using the following analytic approach:

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

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

9.3.6. Outcome Variables

Outcome variables will be identified via a prospective module which is added to the core trunk of the UR-CARE platform to allow for collection of these variables. They will be identified as events of interest and a flag system will alert the study team when they are reported by the site.

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

Primary endpoints

- Malignancy excluding NMSC
- VTE (DVT and PE)

Secondary endpoints

- NMSC
- Lung cancer
- Lymphoma (including 3 main subtypes Hodgkin's lymphoma, non-Hodgkin's lymphoma, and chronic lymphocytic lymphoma)
- Serious infections
- Opportunistic infections (e.g., tuberculosis)
- HZ
- MACE
- MI
- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Fractures
- All-cause mortality

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

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

9.4. Data sources

9.4.1. UR-CARE platform

The United Registries for Clinical Assessment and Research (UR-CARE) was launched on 15 April 2019 and aims to bring the IBD community together at a pioneer level while providing scientific independence at the same time: the initiative is building on the sovereignty of the participating centers and of the permanently established study groups to decide about their data and projects and offer to bring research to an international level.

UR-CARE offers a solid basis for cross-national research and improvement of quality of care for patients' merits because it is thoroughly prepared, transparent and embedded within the academic framework of the European Crohn's and Colitis Organization (ECCO), with a primary focus on users and patients. The commitment to diligence and to scientific integrity are distinctive benchmark characteristics of this project:

- UR-CARE platform is an online EU platform capturing IBD patients' records
- UR-CARE is designed for daily clinical practice and research studies
- UR-CARE is available to study groups and to individual centers

As of November 2021, the UR-CARE platform currently contains information on over 4000 patients diagnosed with IBD.

UR-CARE has been adopted by several IBD National Study Groups. Some groups, such as in Bulgaria (IBD-BG – *Inflammatory Bowel Disease*) and Belgium (BIRD – *Belgian Inflammatory Bowel Disease Research and Development* Group), are using UR-CARE directly as a national database, while in Spain (ENEIDA - *Nationwide study on genetic and environmental determinants of inflammatory bowel disease*) and the Netherlands (ICC - Dutch *Initiative of Crohn's and Colitis*), the existing national databases will be synchronised into UR-CARE in the future (for centers that participate in the ENEIDA registry, synchronization to UR-CARE occurs only if consent is provided. Additionally, if synchronized with UR-CARE, these centers will still use ENEIDA and their data will be synced on a daily basis to the UR-CARE platform so they are not entering data into UR-CARE. The only data that the Spanish investigators from ENEIDA centers will be introducing directly onto the UR-CARE platform is the prospective module, which is exclusive for this study). Note that discussions with the Dutch ICC are still ongoing, and a final agreement is yet to be reached. For all countries participating in UR-CARE, it is also

possible to directly enter data onto the platform on an individual basis for sites that do not belong to a national study group or if the study group does not wish to share their existing national database. Data from these countries will be linked to UR-CARE for any patient who has given informed consent.

Additional details regarding the national IBD study groups that have currently adopted the UR-CARE platform are provided in the subsequent sub-sections.

9.4.1.1. IBD-Bulgaria Group

The IBD-Bulgaria Group was created in 2003 in order to contribute to improve the diagnosis and treatment of IBD in Bulgaria. The association carries out public benefit activities and presents the problems of IBD to Bulgarian authorities and public organizations such as the Ministry of Health, National Health Insurance Fund, etc. The IBD-Bulgaria Group does not currently have a national IBD database; however, the group will use the platform provided by UR-CARE to directly enter IBD patient data from multiple centers in Bulgaria. Patient data to be captured on the UR-CARE platform will include patient demographic and clinical characteristics, IBD treatments, patient comorbidities, etc.

9.4.1.2. Dutch Initiative on Crohn and Colitis

The Dutch Initiative on Crohn and Colitis (ICC) Registry was developed in 2014, and is a nationwide registry for IBD patients starting novel therapies in standard care with a systematic follow-up protocol. The primary objective of the registry is to collect real-world data in a systematic, uniform and prospective manner in order to interpret the effectiveness and safety outcomes of new therapies in IBD. IBD patients aged 16 years or older are included in eight university and seven non-university hospitals[14]. The patients are followed for 2 years with planned visits at initiation of therapy (baseline) and during maintenance therapy (at weeks 12, 24, 52 and 104 or until medication is discontinued). When an eligible patient is identified, a patient information form will be distributed, and IC obtained. Data are captured using electronic case report forms (eCRF) with automated reminders to ensure adherence to the protocol[14]. The eCRF is filled out by the treating physician or IBD nurse at every visit.

While discussions between the ICC and the UR-CARE steering committee are still ongoing and no commitment has been made, it is anticipated that approximately 20 centers, specialized in IBD will participate in this project, each treating roughly 30 patients with novel IBD medication in academic centers and 10 patients in district hospitals a year.

9.4.1.3. BIRD Group

The primary goals of the BIRD Group are to stimulate research in IBD, improve clinical and scientific knowledge of IBD and to stimulate high quality IBD care in daily practice by providing support and education to healthcare professionals. The BIRD Group is building a national database to collect epidemiological data about IBD in Belgium and data on the use of biological therapies in the treatment of IBD. The BIRD Registry will use the platform

provided by UR-CARE, and data will be used to perform retrospective studies and to obtain a comprehensive overview (summary reports) of IBD characteristics/demographics at a national level. As of January 2022, data of more than 1000 patients from 12 centers have already been entered in UR-CARE. In the first quarter of 2022, 13 additional centers collectively joined the BIRD registry study. This includes all Belgium academic centers and most major non-academic hospitals in this country. Information collected as part of the BIRD registry to be entered on the UR-CARE platform include patient demographic and clinical characteristics, surgical and pharmacological treatments, pregnancy and comorbidities/disease complications.

9.4.1.4. ENEIDA

The ENEIDA registry is a large, prospectively maintained nationwide IBD database, promoted by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU)[15]. It was developed in 2005 with the following primary goals: to facilitate the collection of clinical data of interest for clinical care practice, as well as to carry out collaborative studies using clinical data and biological samples[15]. Data such as clinical characteristics, outcomes, and treatments (both pharmacological and surgical) in the ENEIDA registry are entered and/or modified by local investigators on a voluntary basis, although the database is maintained under continuous external monitoring for completeness and consistency of the data entered (ie, the patient data entered in the database is regularly monitored against the patient file). Thanks to the joint work of 380 collaborators, in March 2022 there are 76,369 patients included in 96 participating centers.

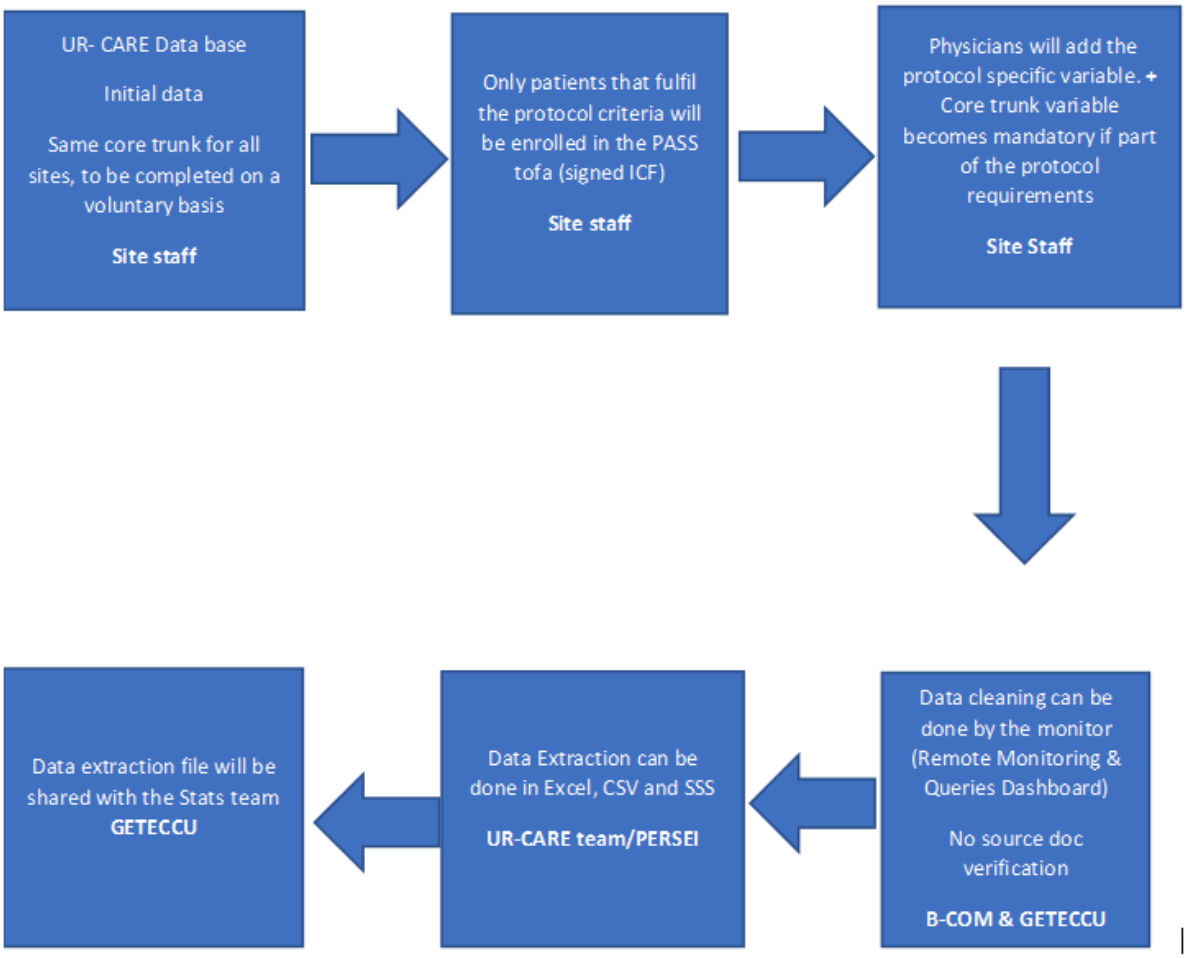
9.4.2. Data entry into the UR-CARE platform

9.4.2.1. Direct data entry via HCPs

As noted above, data are entered on the UR-CARE platform in two ways. Firstly, data are entered on the UR-CARE platform by treating physicians for all IBD patients. Only site staff have full access to patients' identifying information. Patients are requested to sign an informed consent form (ICF) to allow their anonymized data to be used retrospectively, and only a limited set of items are mandatory for physicians to complete. UR-CARE offers clinical investigators the opportunity to easily cooperate across projects, using information captured in the database for multiple projects. Investigators will be able to use the database for retrospective as well as prospective data collection and evaluation, using sophisticated and user-friendly data export and report functions.

Figure 1 below describes the data processing and transformation employed by UR-CARE.

Figure 1. Data processing and transformation.



9.4.2.2. Data linkage for existing data from joining national IBD registries into the UR-CARE platform

The UR-CARE platform will also contain patient data that have been imported from existing national IBD databases such as ENEIDA via a synchronization process ((synchronization will occur prior to the start of data collection for the PASS). The process of data linkage will depend on the variables included in each of the national databases. In principle, every tentative synchronization will follow the same process and rules, except in those cases where any legal requirement or compliance policies may demand differently. The process for data linkage for ENEIDA is outlined below.

The synchronization process follows certain rules agreed with GETECCU and ECCO (the coordinators of the UR-CARE platform) for its correct implementation.

1.- The information sent between both platforms consists only of the necessary for clinical research studies, eliminating patients' direct identifiers and sensitive data and pseudonymizing relevant dates.

2.- The synchronization establishes a relation between the variables and the possible values for those variables on both platforms. A set of rules following a defined criteria allows to technically do the mapping between the variables on one platform (origin) and the other (destination), as agreed and reviewed with both related societies for each platform. These rules were typified as follows: `DIRECT`, `SIMPLE_REP`, `REP_SIMP`, `DIRECT_UPDATE`.

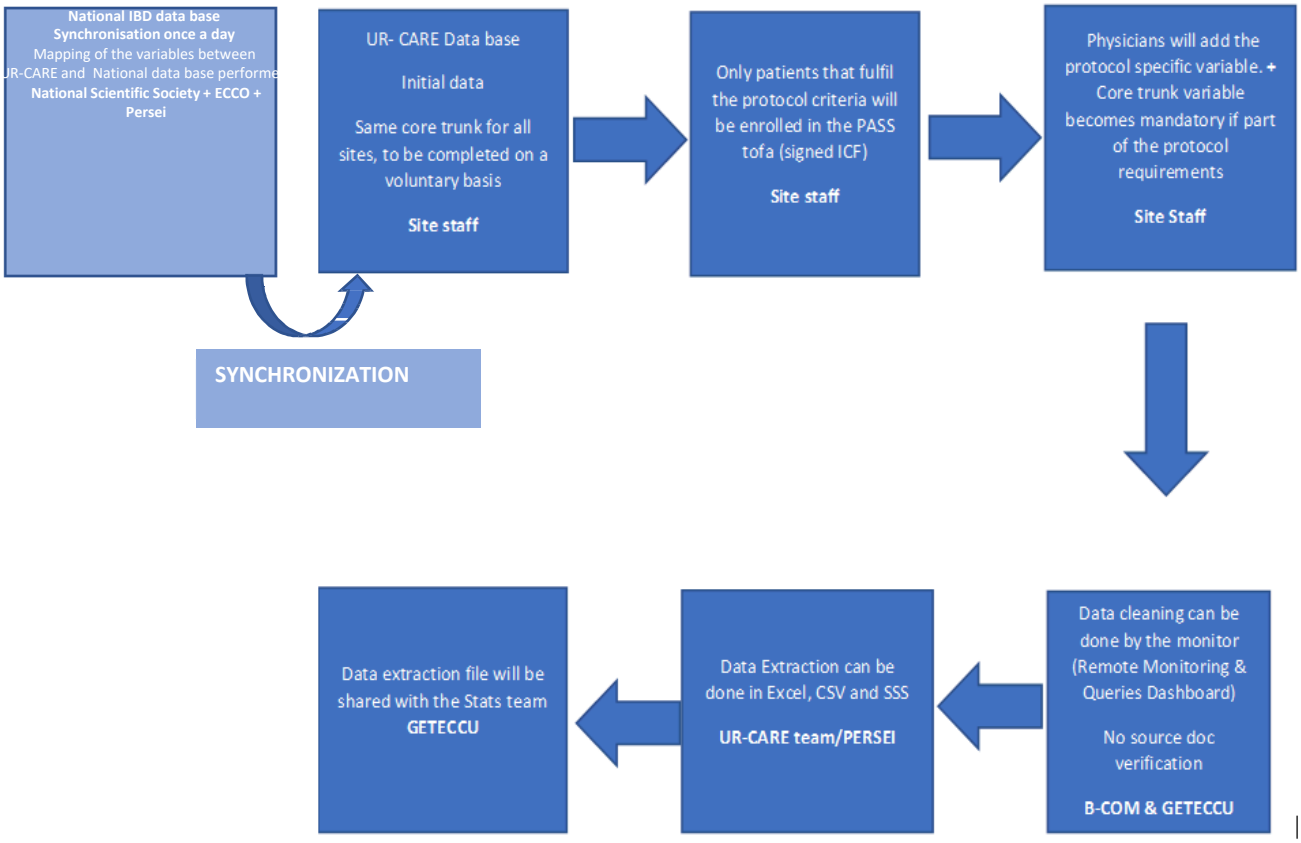
- `DIRECT`: When a local record is created a remote record is created. When the local record is edited, the related remote record is edited.
- `SIMPLE_REP`: Simple to repeatable sync. When a local record is created a remote record is created. When the local record is edited, a new remote record is created too.
- `REP_SIMP`: Repeatable to simple sync. When a local record is created a remote record is edited (if not exists it will be created). When a local record is edited, no action is done.
- `DIRECT_UPDATE`: When there are fields in different forms from local project sync to a unique form in remote project. The record is created in the first config (first form of local project) and then updated with the info sync in the second form of local project.

3.- The process will synchronize only the information of the centers which had previously given their express consent (the synchronization process is not mandatory for ENEIDA centers. Only centers that consent to do so will sync their data to the UR-CARE platform).

Once a final agreement is reached, the process of synchronization of other national IBD databases, such as the Dutch Initiative of Crohn’s and Colitis (ICC), will follow a similar process.

Figure 2 provides details of the process of data linkage for existing data from joining national IBD registries such as ENEIDA into the UR-CARE platform. As noted above, a similar process will be implemented for other national IBD registries in the future.

Figure 2. Process of data linkage for existing data from joining national IBD registries into the UR-CARE platform using the process for ENEIDA as an example



Once the synchronization process is complete, only patients meeting the study-specific inclusion criteria will be included in this PASS. HCPs will then be prompted to complete the prospective module which collects protocol-specific variables. Completion of the core trunk variables will also become mandatory if any of the variables in this module are also required for this PASS. Data cleaning will be conducted by the contract research organization (no source document verification will take place as UR-CARE does not have the capability to independently check the accuracy and consistency of the data in these databases). At the data cut-off points for the interim and final study reports, data extraction will be done using the following programs: Microsoft Excel, CSV and CSS, and the extracted data file will be shared with the statistical team for data analysis.

9.4.3. UR-CARE FOR DAILY CLINICAL PRACTICE

UR-CARE allows capture of the characteristics of Inflammatory Bowel Diseases (IBD) of patients, including biomarkers, imaging and endoscopy indices, as well as treatments and safety aspects. For daily clinical practice, UR-CARE offers comprehensive data collection to local centers for patients diagnosed with Crohn's Disease, Ulcerative Colitis and unclassified colitis through extensive forms that capture information on:

- Disease Characteristics
- Diagnosis (magnetic resonance imaging [MRI], endoscopy, ultrasound, laboratory values, etc.)
- Treatments
- Outcome of the disease (disease evolution)
- Co-existing conditions (pregnancy, related diseases, etc.)
- Other information linked to the patient's condition (complications including infections, cancers, allergies, clinical trials, etc.)

Once the patient file has been created, the physician can easily navigate through the different forms and fill in the variables relevant to the patient. There is a limited number of required variables; further clinical information can be entered in the relevant forms as necessary.

Using the Follow-Up form, the physician can enter further clinical information collected during consultations (e.g. laboratory tests and general condition of the patient) whilst having an overview of the latest procedures (such as last: endoscopy, imaging, surgical treatments, active treatments, etc.).

It is possible to download both short summaries and detailed customized reports of their data. These reports can be downloaded in either PDF or Word format. UR-CARE also offers an export function into Excel file and aims to offer SPSS export in a second stage.

9.5. Study size

The primary analysis is descriptive and all eligible patients in the UR-CARE platform during the study period will be included, with no upper limit on the sample size.

The feasibility of more refined comparative analyses to evaluate safety endpoints that adequately adjust for potential confounders will be assessed and reported in the interim report, and at study end will be based on statistical power as described below. Since the comparator cohorts are expected to be a magnitude larger than the tofacitinib-treated cohort, statistical power will be limited by the uptake of tofacitinib (which is difficult to estimate a priori), as well as the availability of suitable patients in the comparator cohorts.

In Table 1 and Table 2 below, assuming different scenarios of 500 and 1000 patients exposed to tofacitinib, the minimum relative risk between cohorts that could be detected with at least 80% power at the 5% significance level are summarized. Based on the estimates presented in Table 1, assuming 0% annual rate of switching from tofacitinib to another biologic (any

TNFi or non-TNFi), and 0% annual rate of switching from another biologic (any TNFi or non-TNFi) to tofacitinib, for an event with a rate of 5.39/1000 PY, such as malignancy (based on data available in published literature from UR-CARE participating countries), a sample sizes of 500 and 1000 tofacitinib-treated patients would allow for relative risks of 2.2 and 1.9, respectively, to be detected between the tofacitinib and another biologic (any TNFi or non-TNFi) cohorts. For an event with a rate of 2.4/1000 PY, such as VTE (based on data available in published literature from UR-CARE participating countries), sample sizes of 500 and 1000 tofacitinib-treated patients will allow for relative risks of 3.1 and 2.4, respectively, to be detected between the cohorts.

In Table 2, assuming a 30% annual rate of switching, the detectable relative risks between the tofacitinib and the biologics cohorts at 80% power and α= 0.05 are higher (i.e., for malignancy), sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 7.2 and 5.1, respectively, while for VTE, sample sizes of 500 and 1000 tofacitinib-treated patients will allow for detectable relative risks of 13.3 and 8.7, respectively.

Based on these estimations, comparative analyses will be performed if there are ≥500 patients in the tofacitinib cohort, which would allow for between 2.2 to 13.3 relative risk to be detected with 80% power at the 5% significance level, assuming 0% to 30% annual switching between tofacitinib and the biologics cohorts.

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

Assumptions

- α=0.05
- Power=0.8
- Estimated number of IBD patients with TNFi exposure: n= 2386[29] (based on data available from published literature from UR-CARE participating countries)
- 2 different tofacitinib treated patient population sizes: n=500, n=1000
- Estimated rate of malignancy in IBD patients of 5.39/1000 PY[30]; Estimated rate of VTE in IBD patients 2.4/1000 PY[31] (based on data available from published literature from UR-CARE participating countries)
- 7-year total study duration (6 years patient accrual, and minimum 1-year follow-up for last enrolled patient)
- Constant rate of accrual
- 5% annual loss to follow-up among tofacitinib treated patients, and 5% annual loss to follow-up among biologic-treated patients.

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

Table 1. Detectable Relative Risk Among Tofacitinib-Exposed Patients Compared with biologic-exposed IBD Patients with 80% Power, alpha = 0.05, 7-year Study with 6 Years Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, by Safety Event and Tofacitinib Sample Size

Number tofacitinib-treated patients	Estimated rates of safety event while on biologic	Statistical Power	Detectable RR (at 5% significance level)
	Malignancy excluding NMSC		
500	5.39/1000 PY	80%	2.2
1000	5.39/1000 PY	80%	1.9
	VTE		
500	2.4/1000 PY	80%	3.1
1000	2.4/1000 PY	80%	2.4

IBD = inflammatory bowel disease; RR = relative risk

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

Table 2. Detectable Relative Risk Among Tofacitinib-Exposed Patients Compared with biologic-exposed IBD Patients with 80% Power, alpha = 0.05, 7-year Study With 6 Years Uniform Accrual, 5% Loss To Follow Up Per Year In Tofacitinib Arm, by Safety Event and Tofacitinib Sample Size

Number tofacitinib-treated patients	Estimated rates of safety event while on biologic	Statistical Power	Detectable RR (at 5% significance level)
	Malignancy excluding NMSC		
500	5.39/1000 PY	80%	7.2
1000	5.39/1000 PY	80%	5.1
	VTE		
500	2.4/1000 PY	80%	13.3
1000	2.4/1000 PY	80%	8.7

IBD = inflammatory bowel disease; RR = relative risk

9.6. Data management

This study analyzes data consisting of the ongoing UR-CARE platform. The study researchers are responsible for the data management of this study, which will follow the process outlined below:

- Only data from patients who accepted to participate by signing a specific ICF will be available for analysis
- Data completion will be monitored by B-COM Project Manager (PM) on a regular basis

- Data will be filtered by the PM and extracted for analysis (an interim report and final report)

- All patients with a minimum of 80% data completed will be added to the analysis

9.7. Data analysis

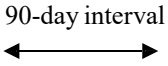
Baseline demographic and clinical characteristics for each cohort, including proportion of patients with ≥1 VTE risk factors will be described. The general analytic approach will be descriptive. For all the safety events of interest, descriptive statistics, counts and proportions, unadjusted cumulative incidence proportions, and crude incidence rates (i.e., number of events per person-years) and age/sex standardized incidence rates with associated 2-sided 95% confidence intervals will be calculated as appropriate.

The estimated incidence rates will be based on survival analysis of time to first event based on an index date defined for each cohort with appropriate censoring rules applied for those who do not experience an event by end of follow-up period (i.e., as described in Section 9.3.4, for a given safety event of interest, patients will be followed from index date until first occurrence of that safety event of interest, treatment switch or discontinuation, with the appropriate outcome-specific extension to exposure depending on type of event [as described below], and with death and end of data collection treated as censoring events). Rates will be expressed as number of events/1000 person-years of follow-up.

9.7.1. Analytic approach for acute safety events

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

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



|----------)----|---x)---*+++++++++|----------x+++++++++
Index date 1 (1st biologic initiation) **Index date 2** (tofacitinib initiation) **Index date 3** (2nd biologic initiation)

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

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

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

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

9.7.2. Analytic approach for malignancy and all-cause mortality events

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

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

While several studies have compared a "once-exposed always at risk" approach to a time on drug and other approaches and found similar rates of malignancy using an on-drug and ever exposed approach[22,23,24,25], the primary analysis for this study will employ the "once-exposed

always at risk" paradigm. Under this approach, follow-up for each cohort continues from the cohort index date until the first malignancy event, loss to follow-up, death or end of study. Follow-up for each exposure cohort will continue even after switching to a new drug in a different exposure cohort or discontinuation of treatment. This approach maximizes follow-up time and the ability to capture long latency events, i.e., events that occur or are detected months to years after exposure. Events will be double-counted if a patient indexed to a biologic switches to tofacitinib and a malignancy occurs subsequent to tofacitinib exposure. That is, the event will be assigned to both the biologic and the tofacitinib exposure cohorts as will the corresponding person-years since index to the respective cohorts. Tofacitinib is expected to be used in patients who have failed at least 1 other advanced systemic therapy. As such, switching is expected to be non-random with most tofacitinib patients having been included in the biologic cohort prior to initiation of tofacitinib. In such cases, the biologic rate will have more associated person-years and thus a relatively lower rate than the corresponding rate in the tofacitinib cohort.

Using this primary analytic approach, if neither tofacitinib nor biologics are associated with an increased risk of malignancy excluding NMSC, both exposure cohort rates will reflect the background rates of malignancy from the time of index to the end of the study period and a comparative effect measure will indicate no difference in rates. If tofacitinib is associated with an increased risk of malignancy excluding NMSC, a relatively higher rate will be observed in the tofacitinib-exposed cohort. The "once-exposed always at risk" approach is therefore able to detect an increased rate given the non-random switching expected to occur given use of biologics prior to tofacitinib and is consistent with previous studies evaluating the risk of individual biologics[22,23,24,25].

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

9.7.3. Sensitivity analyses

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

As an additional sensitivity analysis for acute events for which the primary analysis is the "as-treated approach" with a 90-day extension period applied after treatment discontinuation (as described above in Section 9.7.1), if a new medication is started during the 90-day window after discontinuation of a previous medication, initiation of the new medication will stop the 90-day risk window, and any event prior to the new medication start will be assigned to the discontinued medication. As well for malignancy and all-cause mortality events, a 90-day risk window will be applied to the censoring at switch approach (i.e., if a malignancy or death occurs in first 90 days after a patient has switched to a different therapy, follow-up time and the event will be attributed to prior therapy and not current therapy).

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

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

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

a. Patients continue to be followed after index exposure discontinuation if they do not initiate another systemic therapy in a different class.
b. Patients are ineligible for biologic cohort index after tofacitinib index.

Note: if an event does not occur, person time will be allocated to rate denominator as described in table without corresponding event.

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

Several subgroup analyses will be performed for the primary and secondary safety events of interest. If, for a given subgroup, the sample size does not justify performing a comparative analysis as described in Section 9.5 only descriptive analyses will be performed wherein the crude and age-adjusted rates will be presented along with 95% confidence intervals for the tofacitinib and comparative cohorts. In that case, no significance testing or additional modeling will be performed between the subgroups.

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

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

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

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

For the outcomes of malignancy, excluding NMSC, lung cancer, MACE and MI, incidence rates for the tofacitinib cohort will be estimates overall and stratified by the following:

- Smoking status (current smoker vs. former smoker vs. never smoker, pending sample size feasibility)

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

If feasible, other stratified analyses such as the estimation of the incidence rates for VTE stratified by time periods defined by the changes in the SmPC for tofacitinib use in patients with VTE risk factors will also be conducted (i.e., time period prior to 31 January 2020 vs. time period after 31 January 2020).

9.7.5. Comparative analysis

The feasibility of conducting comparative analyses will be evaluated at an interim time point (as discussed in Section 9.5), and at study end based on statistical power. However, as described in Section 9.5, the actual comparative analyses will only be performed at time of the final report if there are ≥500 patients in the tofacitinib cohort, which would allow for between 2.2 to 13.3 relative risk to be detected with 80% power at the 5% significance level, assuming 0% to 30% annual switching between tofacitinib and biologic cohorts.

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

All statistical analyses will be performed by UR-CARE researchers using SAS version 9.4 (Cary, NC). Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the SAP, which will be dated, filed and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.6. Propensity Score Methods for Propensity Score Trimming and Matching

As discussed above, comparative analyses will be adjusted for differences in severity of disease and other confounders will be completed using propensity score matching methods. This will be conducted in 2 ways: matching and trimming. The steps for determining the propensity score trimmed populations will be as follows:

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

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

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

9.7.7. Interim Report

The interim report will be descriptive and will estimate the crude incidence rates (with corresponding 95% confidence intervals) of safety events of interest by cohort. Additionally, the feasibility of conducting any confounding-controlled comparative analyses will be evaluated based on the observed tofacitinib sample size at the data cut-off date for this report. A comparison of patient baseline characteristics, drug exposure and safety endpoints of interest will also be conducted between similar cohorts for the different data sources used by UR-CARE (i.e., data as entered directly by HCPs through the UR-CARE platform will be compared with data as linked from each of the joining national IBD registries).

9.7.8. Final Study Report

The final study report will include descriptive and, if there is sufficient tofacitinib sample size, detailed results of all comparative analyses and stratifications as outlined above. A comparison of patient baseline characteristics, drug exposure and safety endpoints of interest will also be conducted between similar cohorts for the different data sources used by UR-CARE (i.e., data as entered directly by HCPs through the UR-CARE platform will be compared with data as linked from each of the joining national IBD registries). As well, data from each of the joining national IBD registries will be evaluated for completeness with regards to essential data elements (i.e., drug exposure and safety endpoints) for this PASS, and additional sensitivity analyses will be conducted excluding data from low-quality sources during the final analyses (descriptive, comparative analyses, and stratifications), if warranted.

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

9.8. Quality control

This study uses data existing within the UR-CARE platform. Quality control procedures are defined to ensure the quality of the data that is collected. The Sponsor's contractor, B-COM, will check the consistency, accuracy, and completeness of collected data. The B-COM Project Manager is responsible for regular audits of the data collected on the platform for data quality control purposes.

The following elements are in place to ensure **consistency** and **accuracy** of study information collected:

- Treating physicians will be trained on completion of UR-CARE forms. Annual feedback meetings are organized with the B-COM team with the goal to provide the opportunity to discuss field work problems, communication and information issues.
- The same data elements will be captured for all patients enrolled in the PASS.
- Information can be entered into the platform at any time; however, physicians will be reminded at the end of each year to ensure information is complete for each PASS patient and linkage to external data sources will occur routinely.
- Data entry is standardized with pre-specified formatting for each variable (ie, numbers, integer, decimals, date, strings), preventing inconsistencies (eg, contradictions or value impossibilities) in data entry.
- For any data received by UR-CARE from a national existing IBD registry that requires mapping of data to UR-CARE, processes will be put in place to monitor and verify the accuracy of the data transfer process.

The following elements are in place to ensure **completeness** of data entry:

- UR-CARE has data verification tools (eg, different data entry edit checks, rules, and constraints) to inform on completeness of data entry for a particular patient, as well as an audit system allowing full control of all the changes applied in a specific field.
- Although for study purposes all data entry fields are considered mandatory, it is possible to activate a functionality where the form can be saved without completing the mandatory data entry and leave it to be filled at a later time (saving enabled). In this case, the platform has a pending data dashboard that informs what percentage of the data fields have been completed by the physician for each study patient. Further, to enhance data quality and completeness, selection fields will be available to allow the treating physician to indicate if requested information is not applicable, or unknown to indicate that the fields were not missed by the treating physician during data entry.

- UR-CARE collects information on patient discontinuation or withdrawal from the study.

All data will be stored in secure back-end servers located within the European Union. All sensitive information will undergo a multi-level cyphering process as soon as entered into the database. The information technology (IT) company in charge of designing UR-CARE is compliant with all relevant EU Information Security Management System and Software standards and holds Information Security Standard and Software Process Improvement and Capability Determination certificates.

9.9. Limitations of the research methods

This study is designed to monitor the safety of tofacitinib among UC patients within the clinical practice setting using data from the UR-CARE platform, a multi-national, EU IBD platform. UR-CARE offers access to real-world data on IBD therapy across the EU and allows for the long-term follow-up of IBD patients and their treatment outcomes. Despite the strengths of this study, the possibilities of channeling bias and endpoint misclassification are of concern.

There are several limitations associated with the planned comparative analyses. Firstly, market uptake of tofacitinib will impact the size of the tofacitinib cohort, which cannot be determined a priori. Additionally, as this is a 7-year study, changes in the treatment landscape (e.g., approval of new medications for UC treatment) may further limit the size of the tofacitinib cohort. There is also a lack of a suitable comparator for the tofacitinib cohort. As tofacitinib is a new UC medication, it is likely that patients treated with it will represent those with the most severe cases of disease, longer disease duration, history of multiple failed UC therapies and physical comorbidities that place patients at risk for events. Also, as per the EU SmPC, tofacitinib is to be prescribed to UC patients who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Thus, it is expected that the majority of patients receiving tofacitinib are likely to have cycled through multiple therapies, and may have previously failed at least 1 biologic UC therapy. Channeling may present as increased rates of safety events of interest. Incidence rates from the other UC cohorts may illuminate such channeling via stratification on key indicators of disease severity such as number of previous biologic treatments, patient characteristics and past therapies. As such, statistical power will also be limited by the ability to find suitable patients in the comparator cohorts. This increases the likelihood of residual confounding which could make results from a comparative analysis difficult to interpret. Residual confounding is also a limitation for the comparison of 5 mg vs. 10 mg BID maintenance regimens for tofacitinib since, as per the SmPC, for UC patients who are not at increased risk for VTE, the 10 mg BID dose may be considered only if the patient experiences a decrease in response on 5 mg BID dose, and failed to respond to alternative treatment options for UC such as biologics. As such, patients on the 10 mg BID maintenance dose are more likely to have disease that is harder to treat compared with patients on the 5 mg BID maintenance dose.

UR-CARE employs secondary data collection; as such the data collection methods are similar for both retrospective data collection (ie, data from patients starting tofacitinib prior to the study's start date of data collection) and prospective data collection (ie, data from patients starting tofacitinib after the study's start data of data collection). While it is possible for there to be a higher level of data missingness from patients that have begun treatment prior to the PASS start date of data collection, given that the UR-CARE platform has been recently established, it is difficult at the time of protocol development to gauge how retrospective data entry will compare to prospective data entry. Additionally, for each national IBD database joining the UR-CARE platform, patient data are entered at the local level by participating sites/investigators. As these databases are nationwide, they are each representative of the IBD population in each country. Each national database or individual site is responsible for checking the accuracy and consistency of the data in their respective databases. Data are generally verified via patient medical records at the local level. However, UR-CARE does not have the capability to independently check the accuracy and consistency of the data in these databases. Additionally, there will be differences in the type of data collected for each data source that is linked to the UR-CARE platform; however, the prospective module of the UR-CARE platform which is adapted for each new research study will ensure that study-specific endpoints and treatments are captured similarly across the various data sources. As well, while efforts are made to ensure that all variables in the prospective module are completed, it is possible to have missing data due to a particular variable not being collected in a specific data source. However, the rate of missingness in such instances cannot be estimated.

Certain patient characteristics which may influence VTE outcomes (e.g., smoking status, obesity and immobilization), are not well captured in UR-CARE, and thus may limit data interpretation. While immobilization may not be captured completely in UR-CARE, including inpatient care due to UC (i.e., UC as main diagnostic listing), the platform will capture hospitalized patients who will have reduced/limited mobility, and who will therefore be at a potentially higher risk for VTE (consensus guidelines recommend thromboprophylaxis for all admitted patients with IBD in the absence of contraindications[16]). While the use of the proxy "inpatient care because of UC" will allow for patient immobilization to be taken into account in the analysis, length of hospitalization due to UC, which can impact a patient's risk for VTE, cannot be adequately accounted for in the analysis as it is not well captured in UR-CARE. Inherited coagulation disorders encompass a broad range of conditions, and only a limited number of these can be reliably captured. Other VTE risk factors such as major surgery, MI within previous 3 months prior to index date, heart failure, diabetes, hypertension, malignancy and age are well captured in the UR-CARE platform.

Event misclassification is of particular concern in a routine healthcare setting due to less stringent monitoring relative to clinical trials. Additionally, other factors such as errors in recording also need to be considered.

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

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

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

Patient personal data will be stored on the UR-CARE platform in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. B-COM 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, B-COM shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract and applicable privacy laws.

10.2. Patient consent

This study involves the use of secondary data collected as part of the UR-CARE platform. As part of UR-CARE standard procedures, collection of data for all new research studies, as is the case here, requires informed consent from the patients prior to participation as described in Section 9.2.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The scientific purpose, value and rigor follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology, and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA) and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

An interim report will be generated. The interim and final study reports will be submitted to regulatory authorities. Manuscripts based on specific endpoints of interest may be developed for publication purposes and EMA will be notified upon acceptance for publication. Additionally, both study protocol and final study report will be posted on the EU PAS register.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. BMJ 2013; 346:f432

2. Burisch J, Pedersen N, Čuković-Čavka S, et al. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. Gut 2014;63(4):588-97.

3. Sjöberg D, Holmström T, Larsson M, et al. Incidence and natural history of ulcerative colitis in the Uppsala Region of Sweden 2005–2009 — Results from the IBD Cohort of the Uppsala Region (ICURE). Journal of Crohn's and Colitis. 2013;7(9):e351-e357

4. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142(1):46-54.

5. Büsch K, Ludvigsson JF, Ekström-Smedby K, et al. Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. Aliment Pharmacol Ther. 2014;39(1):57-68.

6. The Committee for Medicinal Products for Human Use. Guideline on the development of new medicinal products for the treatment of ulcerative colitis. CHMP/EWP/18463/2006 Revision 1. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development- new-medicinal-products-treatment-ulcerative-colitis-revision-1_en.pdf

7. Coward, S., Clement, F., Benchimol, E. I., et al. (2019). Past and Future Burden of Inflammatory Bowel Diseases Based on Modeling of Population-based Data. *Gastroenterology*. http://doi.org/10.1053/j.gastro.2019.01.002

8. Dahlhamer JM, Zammitti EP, Ward BW, et al. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years — United States, 2015. MMWR Morb Mortal Wkly Rep 2016; 65(42):1166–1169.

9. Everhov, Å. H., Halfvarson, J., Myrelid, P., Sachs, M. C., Nordenvall, C., Söderling, J., et al. (2018). Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. Gastroenterology. 154(3), 518–528.e15.

10. Khalili, H., Söderling, J., Everhov, Å. H., et al. 15 - Health Care Use, Work Loss, and Total Costs in Incident and Prevelant Ulcerative Colitis: Results from a Nationwide Study in Sweden. Gastroenterology 2018, 154(Supplement 1), S–5–5. http://doi.org/10.1016/S0016-5085(18)30504-3

11. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367(7):616-624.

12. Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006;130(3):940-987.

13. McAuliffe ME, Lanes S, Leach T, et al. Occurrence of adverse events among patients with inflammatory bowel disease in the HealthCore Integrated Research Database. Curr Med Res Opin. 2015;31(9):1655-1664.

14. Ludvigsson, J. F., Svedberg, P., Olen, O., et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research.

15. European Journal of Epidemiology 2019; 1–15. http://doi.org/10.1007/s10654-019-00511-8

16. Biemans VBC, van der Meulen-de Jong AE, van der Woude CJ, et al. Ustekinumab for Crohn's Disease: Results of the ICC Registry, a Nationwide Prospective Observational Cohort Study. J Crohns Colitis. 2020 Jan 1;14(1):33-45. doi: 10.1093/ecco-jcc/jjz119. PMID: 31219157; PMCID: PMC7142409.

17. Zabana Y, Panés J, Nos P, et al. The ENEIDA registry (Nationwide study on genetic and environmental determinants of inflammatory bowel disease) by GETECCU: Design, monitoring and functions. Gastroenterol Hepatol. 2020 Nov;43(9):551-558. English, Spanish. doi: 10.1016/j.gastrohep.2020.05.007. Epub 2020 Jul 14. PMID: 32674882.

18. Murthy SK, Robertson McCurdy AB, Carrier M, et al. Venous thromboembolic events in inflammatory bowel diseases: A review of current evidence and guidance on risk in the post-hospitalization setting. Thromb Res. 2020; 194:26-32

19. Curtis JR, Chen SY, et al. Validation of ICD 9 CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients. Pharmacoepidemiol Drug Saf. 2011; 20(11):1150 8.

20. Brooke, H. L., Holzmann, M. J., Olen, O., et al. Enhancing evidence-based medicine: Twelve tips for conducting register-based research. MedEdPublish 2016; 5(2). http://doi.org/10.15694/mep.2016.000071

21. Bernstein CR, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001; 91(4): 854-862.

22. Jess T, Horvath-Puho E, Fallingborg J, et al. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. Am J Gastroenterol 2013; 108(12):1869-1876.

23. van den Heuval TR, Wintjens DS, Jeuring SF, et al. Inflammatory bowel disease, cancer and medication: cancer risk in the Dutch population-based IBDSL cohort. Int J Cancer 2016; 139(6):1270-1280.

24. Mercer LK, Lunt M, Low ALS, et al Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Annals of the Rheumatic Diseases 2015;74:1087-1093.

25. Mercer LK, Galloway JB, Lunt M, et al. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Ann Rheum Dis 2017;76:497–503.

26. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010;12(1):R5.

27. Wadstrom H, Frisell T, Askling J, et al. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice. JAMA Intern Med. 2017;177(11):1605 1612.

28. Ludvigsson JF, Andersson M, Bengtsson J, et al. Swedish Inflammatory Bowel Disease Register (SWIBREG) - a nationwide quality register. Scand J Gastroenterol. 2019;54(9):1089-1101. doi: 10.1080/00365521.2019.1660799. Epub 2019 Sep 9.

29. Sultan, A., West, J., Stephansson, O., Grainge, M., Tata, L., Fleming, K., Humes, D., Ludvigsson, J. (2015). Defining venous thromboembolism and measuring its incidence using Swedish health registries: a nationwide pregnancy cohort study. BMJ open 5(11), e008864. https://dx.doi.org/10.1136/bmjopen-2015-008864

30. Esposti L, Favalli EG, et al. Persistence, switch rates, drug consumption and costs of biological treatment of rheumatoid arthritis: an observational study in Italy. Clinicoecon Outcomes Res. 2016 Dec 21;9:9 17.

31. Chaparro M, Ramas M, Benítez JM, et al. Extracolonic Cancer in Inflammatory Bowel Disease: Data from the GETECCU Eneida Registry. Am J Gastroenterol. 2017 Jul;112(7):1135-1143. doi: 10.1038/ajg.2017.96. Epub 2017 May 23. PMID: 28534520.

32. Scharl S, Barthel C, Rossel JB, et al. Malignancies in Inflammatory Bowel Disease: Frequency, Incidence and Risk Factors-Results from the Swiss IBD Cohort Study. Am J Gastroenterol. 2019 Jan;114(1):116-126. doi: 10.1038/s41395-018-0360-9. PMID: 30333538.

33. Papa A, Gerardi V, Marzo M, et al. Venous thromboembolism in patients with inflammatory bowel disease: focus on prevention and treatment. World J Gastroenterol. 2014;20(12):3173-3179. doi:10.3748/wjg.v20.i12.3173

14. VARIABLE DEFINITIONS

14.1. Appendix 1 – MedDRA Definitions (English version 24.1)

Event as reported	MedDRA coding (LLT)	MedDRA coding (PT)	SMQ
Malignancy, excluding non-melanoma skin cancer (NMSC);	Cancer of skin (excl melanoma)	Skin cancer	Malignancies

Thromboembolic events	Thromboembolic event	Embolism	Embolic and thrombotic events
Deep Venous Thrombosis [DVT]	Thrombosis venous deep	Deep vein thrombosis	Embolic and thrombotic events, venous
Pulmonary Embolism [PE]	Pulmonary embolism	Pulmonary embolism	Embolic and thrombotic events, venous
Non-Melanoma Skin Cancer (NMSC)	Skin cancer	Skin cancer	Malignancies
Lymphomas	Lymphoma	Lymphoma	Malignancies
Chronic Lymphocytic Leukemia	Chronic lymphocytic leukemia	Chronic lymphocytic leukaemia	Malignancies
Hodgkin Lymphoma	Hodgkin's lymphoma	Hodgkin's disease	Malignancies
Non-Hodgkin Lymphoma	Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma	Malignancies
Lung cancer	Lung cancer	Lung neoplasm malignant	Malignancies
Opportunistic infections (e.g., tuberculosis)	Infection	Infection	Opportunistic infections
Major adverse cardiac events (MACE)	Cardiovascular disorder	Cardiovascular disorder	Cardiomyopathy
Myocardial infarction	Myocardial infarction	Myocardial infarction	Embolic and thrombotic events
Progressive multifocal leukoencephalopathy (PML)	Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy	Opportunistic infections
Gastrointestinal (GI) perforations	Gastrointestinal perforation	Gastrointestinal perforation	Ischaemic colitis
All-cause mortality	Death NOS	Death	
Bone fractures or fissures	Fracture bone / Bone fissure	Fracture bone / Bone fissure	Osteoporosis-osteopenia / Accidents and injury
Previous VTE	Venous thromboembolism	Embolism	Embolic and thrombotic events

Undergoing major surgery from date of hospital admission to one month after date of discharge	Surgery	Surgery	
Myocardial infarction within previous 3 months prior to index date	Myocardial infarction	Myocardial infarction	Embolic and thrombotic events
Heart failure	Heart failure	Cardiac failure	Cardiomyopathy
Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date	Hormone therapy	Hormone therapy	Malignancies
Malignancy	Malignant tumor	Neoplasm malignant	Malignancies
Diabetes	Diabetes	Diabetes mellitus	Immune-mediated/autoimmune disorders
Hypertension	Hypertension	Hypertension	Hypertension
Inherited coagulation disorders	Inherited coagulation disorders	Coagulopathy	Haemorrhages
Smoking status	Smoker	Tobacco user	
Obesity	Obesity	Obesity	Hyperglycemia/new onset diabetes mellitus
Immobilization – Inpatient care because of UC	Hospitalization	Hospitalization	
Immobilization	Immobilization syndrome	Immobilization syndrome	

14.2. Appendix 2 – Overview of Essential Data Elements as captured by direct entry and as captured with joining national IBD registries using ENEIDA as an example

Variable	**ENEIDA (Spain)**	**UR-CARE**
Key patient characteristics		

Variable	ENEIDA (Spain)	UR-CARE
Year of birth	Yes	Yes
Sex	Yes	Yes
Date of initiation of tofacitinib	Yes	Yes
Initial dose of tofacitinib	Yes	Yes
UC treatment immediately prior to initiation of tofacitinib	Yes	yes
Year of UC diagnosis	Yes	yes
Disease location: Proctitis / left-sided colitis / pancolitis	yes (maximum extent reached only)	yes, maximum extent reached
Presence of stoma: y/n	yes	yes
Co-morbidities (previous/recent diagnosis of)		
Serious and opportunistic infections	yes	yes
Herpes zoster and primary Varicella infection	yes (zoster and varicella are usually registered as an AE if the patient is receiving an immunosuppressant or biological therapy)	yes (zoster and varicella are usually registered as an AE if the patient is receiving an immunosuppressant or biological therapy)
Cardiovascular disease or stroke	yes (available from additional data collection [questionnaire])	yes, as comorbidity
VTE (including DVT, PE)	yes (thrombotic events may be registered in ENEIDA as an extraintestinal manifestation, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes, as comorbidity
Hyperlipidemia	yes (hyperlipidemia may be registered in ENEIDA as a general comorbidity, but probably under-	yes (hyperlipidemia may be registered as a comorbidity)

Variable	ENEIDA (Spain)	UR-CARE
	recorded; but could be available from additional data collection [questionnaire])	
Malignancies (excluding NMSC)	yes	yes
NMSC	yes	yes
GI perforation	yes (available from additional data collection [questionnaire])	Can be recorded as a complication
Renal impairment (& stage)	yes (nephropathies may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes (may be registered as a comorbidity)
UC severity		
Simple Clinical Colitis Activity Index (SCCAI)	no	no
General well-being	yes (available from additional data collection [questionnaire])	yes
Stools/day	yes (available from additional data collection [questionnaire])	yes
Nocturnal stools	yes (available from additional data collection [questionnaire])	yes
Blood in stools	yes (available from additional data collection [questionnaire])	yes
Physician Global Assessment (PGA)	yes (available from additional data collection [questionnaire])	Can be collected (i.e., all items are collected for the mayo score but there is no specific field to write the result and it is not automatically calculated. The physician, if he wants to note

Variable	ENEIDA (Spain)	UR-CARE
		the result, has to write it in the "Note" field. But it can also be developed in the prospective module of the study.
Mayo score	yes (available from additional data collection [questionnaire])	Can be collected (ie, all items are collected for PGA but there is no specific field to write the result and it is not automatically calculated. If the physician wants to note the result, it should be written in the "Note" field. But it can also be developed in the prospective module of the study)
Other severity variable (which one?)	yes (CRP, fecal calprotectin [not in all patients but in a great proportion, at least once per year]; available from additional data collection [questionnaire])	yes (hyperlipidemia may be registered as comorbidity)
Date of severity assessment	yes (available from additional data collection [questionnaire])	yes
Health Assessment Questionnaire ([HAQ] or other QoL score)	no	No; it will require prospectively recording
Exposures of interest (including date of 1st administration)		
Tofacitinib (cohort 1)	yes	yes
Advanced therapies (cohort 2)	yes	yes
Immunosuppressants/immunomodulators (cohort 3)	yes	yes
Naïve (cohort 4)	yes	yes
Risk factors for MACE, VTE, serious/opportunistic infections		

Variable	ENEIDA (Spain)	UR-CARE
History of CVD	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes (may be registered as a general comorbidity, but probably under-recorded; but could be available from addition of prospective values)
History of VTE	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes (may be registered as a general comorbidity, but probably under-recorded; but could be available from addition of prospective values)
Previous serious infection	yes (available from additional data collection [questionnaire])	yes (may be registered as a general comorbidity, but probably under-recorded; but could be available from addition of prospective values)
Type 1 diabetes mellitus	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes
Type 2 diabetes mellitus	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes
Atrial fibrillation	yes (available from additional data collection [questionnaire])	yes, as comorbidity
CKD (diagnosis and stage if available)	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Smoking	yes	yes

Variable	ENEIDA (Spain)	UR-CARE
Family history of CVD	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes (may be registered as comorbidity, requires additional variable)
Hyperlipidemia	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes (may be registered as a comorbidity, but could require additional variable
Hypertension	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes, as a comorbidity
Rheumatoid arthritis	yes (may be registered in ENEIDA as a general comorbidity, but probably under-recorded; but could be available from additional data collection [questionnaire])	yes, as comorbidity
Active cancer	yes	yes
Known thrombophilic condition	yes (available from additional data collection [questionnaire])	yes (as comorbidity, but may require additional variable)
Reduced mobility / hospitalization	yes (available from additional data collection [questionnaire])	yes
Trauma and/or surgery	yes (available from additional data collection [questionnaire])	Surgery yes, trauma will require additional variable
Ongoing hormonal replacement therapy	yes (available from additional data collection [questionnaire])	yes

Variable	ENEIDA (Spain)	UR-CARE
Heart and/or respiratory failure	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Acute myocardial infarction or ischemic stroke	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Obesity or BMI	yes (available from additional data collection [questionnaire])	yes
Acute infection and/or rheumatologic disorder	yes (available from additional data collection [questionnaire])	yes
Chronic lung disease	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Treatment failure	yes (available from additional data collection [questionnaire])	yes, indicated by change of medication
Glucocorticoid	yes	yes
TNFα inhibitors and other biologics	yes	yes
Number of prior advanced therapies	yes	yes
Other immunosuppressant/modifying therapy	yes	yes
Additional risk factors		
Thiopurines	yes	yes
Combination therapy	yes	yes
NSAIDs	no	yes, if registered
History of diverticulitis	no	Requires additional variable (ie, medical history is not specified in the UR-CARE platform.

Variable	ENEIDA (Spain)	UR-CARE
		Currently a verbatim field for this event must be completed)
Other GI conditions	no	no
Phototherapy	no	no
Caucasian race	yes	yes
Diet	no	no
Inactivity	no	no
Biliary obstruction	yes (available from additional data collection [questionnaire])	yes
Hypothyroidism	yes (available from additional data collection [questionnaire])	yes
Rheumatoid arthritis	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Familial hypercholesterolemia	no	yes, as comorbidity
Alcohol	yes (available from additional data collection [questionnaire])	no
Family history of cancer	no	no
History of cancer	yes (available from additional data collection [questionnaire])	yes, if recorded
Outcomes of interest		
Serious and opportunistic infections	yes	yes
Herpes zoster and primary Varicella infection	yes	yes

Variable	ENEIDA (Spain)	UR-CARE
MACE (excluding VTE)	yes (available from additional data collection [questionnaire])	yes, as comorbidity
VTE (including DVT and PE)	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Hyperlipidemia	yes (available from additional data collection [questionnaire])	yes, as comorbidity
Malignancies (excluding NMSC)	yes	yes
NMSC	yes	yes
GI perforation	yes (available from additional data collection [questionnaire])	yes
All-cause mortality	yes	yes

15. LIST OF TABLES

16. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance, Post-Authorization Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from the United Registries for Clinical Assessment and Research (UR-CARE) in the European Union (EU)

EU PAS Register® number:
Study reference number (if applicable): A3921352

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

Comments:

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

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

Comments:

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

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	6 & 9.1
	4.2.2 Age and sex	☒	☐	☐	9.2.1 & 9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	8, 9.2.1 & 9.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.3.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1 & 9.2.2

Comments:

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

Comments:

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

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

Comments:

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

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2
9.2.2 Outcomes? (e.g., date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	9.3.6
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	14.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.1

Comments:

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

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

Comments:

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

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

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Nana Koram

Date: 27-February-2023

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

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Rubino, Heather	20-Mar-2023 20:42:12	Manager Approval
De Bernardi, Barbara	21-Mar-2023 12:02:33	EUQPPV Approval