NON-INTERVENTIONAL (NI) PROGRESS REPORT

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 (URCARE) in the European Union (EU)
Protocol number	A3921352
Version identifier of the progress report	1.0
Date	16 February 2026
EU Post Authorization Study (PAS) register number	EUPAS103632
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (Tofacitinib)
Product reference	EMEA/H/C/004214
Procedure number	EMA/PAM/0000247897
Marketing Authorization Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint Post-Authorization Safety Study (PASS)	No
Research question and objectives	Research Question: What are the 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. **Cohorts** - 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
Country(-ies) of study	Multiple European Union (EU) nations using UR-CARE registry (Spain, Greece, Lithuania, Belgium, Bulgaria, Slovenia, Romania)
Author	Jose Montes Garcia Statistician. Head of Biometry Effice Research/Christine Nguyen Demange, CEO of the CRO B-COM

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
MAH contact person	Maureen Agius Pfizer Ltd. Walton Oaks Dorking Road Tadworth Surrey KT20 7NS United Kingdom

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Annex 1. List of stand-alone documents

Appendix 1. Protocol

Appendix 2. Statistical analysis plan

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
RMP	Risk Management Plan
SAP	Statistical Analysis Plan

Abbreviation	Definition
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

INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Yamile Zabana, MD, PhD	Co-Principal Investigator	GETECCU Gran Vía 81, 5to Dept 5, 48001, Bilbao, Spain
Manuel Barreiro, MD, PhD	Co-Principal Investigator	GETECCU Gran Vía 81, 5to Dept 5, 48001, Bilbao, Spain
Nana Koram, PhD, MPH	Safety Surveillance Research Scientist	Safety Surveillance Research, Pfizer, Inc. 66 Hudson Blvd, New York, New York 10001
José Montes García	Statistician	Effice Servicios Para la Investigación S.L. Paseo de la Castellana,127ºD 28046 Madrid

OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
B-COM	Contract research organization responsible for operational management

1. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection*	31 January 2024	24 April 2024	Start of data collection represents the date the data were extracted from the UR-CARE system for analysis of the interim report. Data were extracted later than planned to allow for accrual of additional patients within the UR-CARE system
End of data collection	31 March 2026	NA	NA
Interim report	31 August 2024	31 August 2024	NA
Progress report	28 February 2026	16 February 2026	
Registration in HMA-EMA Catalogues of RWD Studies	Prior to the start of data collection	21 July 2023	NA
Final study report**	31 March 2027	NA	NA

NA – not applicable
*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 March 2026

2. 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[2] 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).

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[3,4,5]. The EMA's Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (Committee for Medicinal Products for Human Use [CHMP]/Efficacy Working Party [EWP]/18463/2006 Revision 1), estimates prevalence to be 70 to 500 cases per 100,000 with peak age of onset between 15 and 25 years. In 15% of cases, UC is diagnosed in childhood and may present before school age[6]. Data from multiple countries suggest increasing prevalence over time[4,7].

UC presents significant health and socioeconomic burdens for the individual patient and society[8-10]. There is currently no cure for UC[1]. Moderate-to-severe UC often requires treatment with systemic agents, such as glucocorticoids and azathioprine[11], as well as biologics many of which are associated with infectious, cardiovascular, gastrointestinal and malignant adverse events[12,13]. Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the European Union (EU) in July 2018 at a dose of 5 mg twice daily (BID) or 10 mg BID for the treatment of adults with moderate-to-severe UC, who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Malignancy excluding NMSC is an important potential risk associated with the use of Tofacitinib. In January 2020, as a result of a reassessment of the benefit-risk of Tofacitinib, the European Commission (EC) approved several revisions to the Summary of Product Characteristics (SmPC), including addition of VTE as an important identified risk associated with the use of Tofacitinib.

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) was to assess the risk of VTE, malignancy excluding NMSC, and other safety events of interest in patients with UC initiating treatment with Tofacitinib in a real-world setting. Incidence rates of the same endpoints were estimated for adult patients with UC treated with other approved systemic medications, as well as adult patients with UC naïve to both biologics and immunomodulators/immunosuppressants, to provide context to the findings.

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

At the request of the EMA, a study progress report is provided. The goal of this progress report (data cut off is 29 September 2025) is to describe the overall representativeness, completeness and quality of the data set, including an evaluation of the availability and coverage of essential data elements for this PASS from the various participating UR-CARE sites that are included by comparing patient baseline characteristics, drug exposure and safety endpoints of interest within similar Cohorts between the sites in the study-specific prospective module of the UR-CARE database.

3. RESEARCH OBJECTIVES

The research question for this study is: What are the incidence rates of safety events of interest in adult 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)

4. RESEARCH METHODS

This progress report was developed with reference to the final protocol (Version 5.0: 16 January 2025; Appendix 1. Protocol).

4.1. Study design

This is a 7-year active Cohort study of adult patients with UC aged ≥18 years treated with Tofacitinib compared to patients receiving alternative treatment or no treatment. The study used secondary data collected in the UR-CARE platform. To allow for a minimum follow-up duration of 12 months, patients with UC meeting the study entry criteria through 31 March 2025 will be included in the analysis for the final analysis, with follow-up of patients for the study ending on 31 March 2026.

4.1.1. 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 on the date of concomitant medication use initiation 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.

4.1.2. 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.

4.1.3. 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]

4.1.4. 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; 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, 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.

4.2. Setting

This secondary data collection study uses data collected as part of 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 focuses only on UC patients enrolled in the UR-CARE platform.

The UR-CARE platform contains medical records, including identifying data, of patients from multiple EU and non-EU countries. The following is a list of UR-CARE 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 participating countries as well as inclusion of new sites or study groups are provided in this progress report. Note that in this progress report, only six of 11 countries mentioned above included patients for this study: Spain, Slovenia, Romania, Bulgaria, Greece and Belgium. This is because as per UR-CARE standard policy, each individual site in each participating country must provide consent to allow access to their data. One additional country, Lithuania, is also included in this report as one site from that country consented to participate due to the ongoing PASS promotion activities.

As per UR-CARE standard process, patients participating in any prospective study using UR-CARE are required to sign a separate informed consent form (ICF) to allow the treating physician to access the study module and capture study specific data such as safety events. The prospective module data became accessible only after the physician had confirmed that patients had signed the study-specific ICF. Data from all patients were entered on the UR-CARE platform, but to protect patients' confidentiality, only anonymized data from those who had accepted to participate in the PASS were provided on the research platform for analysis by the research team.

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

4.3. Subjects

4.3.1. Inclusion criteria

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

1. Patients aged ≥18 years enrolled in the UR-CARE platform

2. Patients with UC diagnosis per European Crohn's and Colitis Organisation (ECCO) guidelines as established by the treating physician were eligible for inclusion. The severity of the disease was confirmed with clinical parameters (such as 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.

4. Patients must have a minimum of 12 months of medical history available either in UR-CARE prior to the index date.

5. Initiation UC treatment (Tofacitinib, specific biologic agent, specific immunosuppressant agent) from 01 July 2018 through to 31 March 2025 or naïve to treatment with UC diagnosis from 01 July 2018 to 31 March 2025.

4.3.2. Exclusion criteria

Patients did not present any of the exclusion criteria to be allowed to participate in the study:

1. Refusing to sign the ICF to authorize utilization of their data.

2. Patients in treatment with other biologics or immunosuppressants or immunomodulators not yet approved for the treatment of UC in the EU. Such patients were 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 final study reports.

3. Patients with prior history or in treatment with other non-Tofacitinib JAK inhibitors.

4. 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) were not allowed.

4.4. Variables

4.4.1. Baseline variables

Physicians enter data from patient medical records to identify non-demographic baseline variables. The baseline period for all Cohorts will be 12 months prior to index date. 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.

4.4.1.1. 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 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
- 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

4.4.2. 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.

4.4.2.1. Duration of exposure

Duration of exposure will be defined in the final report 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.

4.4.2.2. 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 know 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 in the final report 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) was estimated using daily defined dose (DDD).

For time periods 2 and 3, ADD was 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 in the final report.

4.4.3. Outcome variables

Outcome variables were 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 are defined as events of interest and a flag system alerts the study team when they are reported by the site.

The study outcome variables included are described below in the subsequent sub-sections.

4.4.3.1. Primary endpoints

- Malignancy excluding NMSC: All malignancies excluding NMSC
- VTE (DVT and PE)

4.4.3.2. Secondary endpoints

- NMSC
- Lung cancer
- Lymphoma (including 3 main subtypes Hodgkin's lymphoma, non-Hodgkin's lymphoma, and chronic lymphocytic lymphoma)
- Serious infections: defined as hospitalized infections due to the following: Infectious diseases, by type of infectious agent, Spleen abscess, Thyroid abscess, Thymus abscess, Meningitis, Encephalitis, CNS abscess, Eyelid abscess, Purulent eye infection, Infectious external otitis, Otitis media, Mastoiditis, Infectious pericarditis, Infectious myocarditis, Acute infections in upper and lower airways, Chronic sinusitis, Nose abscess, Peritonsillitis Vocal cord abscess, Pharyngeal abscess, Chronic obstructive lung disease with acute lower airway infection, Lung abscess, Pleura empyema, Tooth infections, Osteitis in the jaw, Salivary gland abscess, Mouth abscess, Tongue abscess, Small or large bowel diverticulitis with perforation or abscess, Perianal abscess, Bowel abscess, Peritonitis, Skin infections, Infectious dermatitis, Infectious arthritis, Vertebral infections, Infectious myositis, Infection in tendon sheath, Infectious bursitis, Necrotising fasciitis, Osteomyelitis, Acute infectious glomerulonephritis, Chronic infectious glomerulonephritis, Infectious glomerulonephritis, Pyonephrosis, Renal abscess, Kidney infection, Cystitis, Urethra abscess, Prostate abscess, Hydrocele infection, Orchitis et epididymitis, Penile abscess, Breast abscess, Salpingitis et oophoritis, Infections in the female pelvic organs, Abscess in the Bartholini gland.
- Opportunistic infections: defined as infections due to the following: Salmonella infections, Tuberculosis in airways (verified histologically or microbiologically), Tuberculosis in airways (unverified histologically or microbiologically), Tuberculosis in the nervous system, Tuberculosis in other organs, Tuberculosis miliaris, Mycobacterial infections, Listeriosis, Nocardiosis, Legionnaire disease, Coccidioidomycosis, Histoplasmosis, Blastomycosis, Aspergillosis, Cryptococcosis, Toxoplasmosis, Pneumocystosis.
- HZ
- MACE: Cardiovascular death (death due to MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedure, death due to CV hemorrhage, death due to other CV causes [e.g. peripheral artery disease]); non-fatal MI, non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage
- MI
- PML
- GI perforations
- Fractures
- All-cause mortality

4.5. Study Size

The primary analysis is descriptive and all eligible patients in the UR-CARE platform during the study period were 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 were assessed at the time of analysis for this progress report (and will be re-assessed at study end) and was 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 is 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 2 and Table 3 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 the protocol, 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), 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 allowed 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 allowed for detectable relative risks of 7.2 and 5.1, respectively, while for VTE, sample sizes of 500 and 1000 Tofacitinib-treated patients allowed 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= 238629 (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 PY30; Estimated rate of VTE in IBD patients 2.4/1000 PY31 (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, 0% annual rate of switching from Tofacitinib to biologic, and 0% annual rate of switching from biologic to Tofacitinib 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, 30% annual rate of switching from Tofacitinib to biologic, and 30% annual rate of switching from biologic to Tofacitinib 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

4.6. Data transformation

Detailed methodology for data transformations are documented in the statistical analysis plan (SAP), which is dated, filed, and maintained by the sponsor (Appendix 2. Statistical analysis plan).

5. STUDY PROGRESS

5.1. Subjects

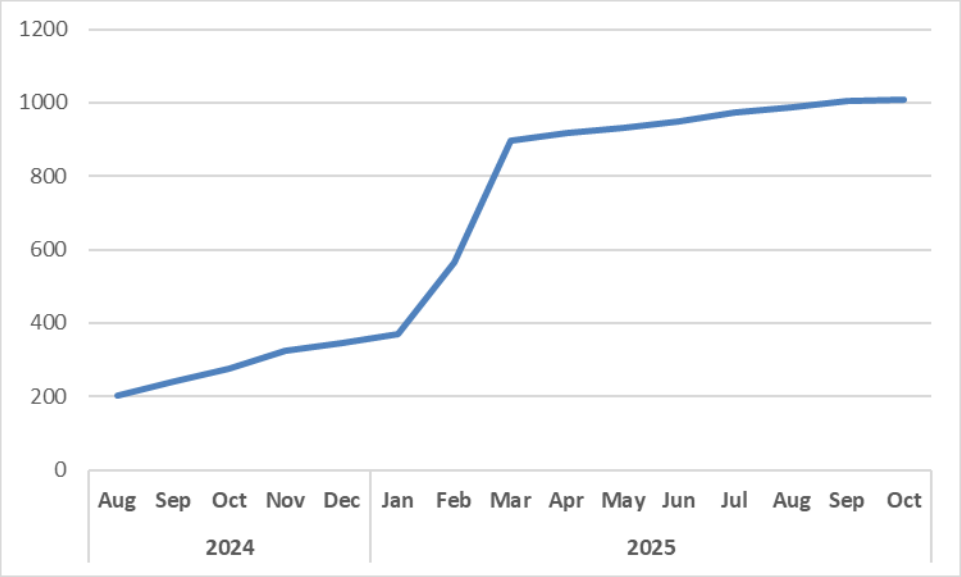
For this progress report, data cut off was 29 September 2025.

There were 1,186 IBD patients in the UR-CARE database of which this study team had consent to access data for 1,157 IBD patients. Of the 1,157 patients, 150 patients were excluded for not meeting the PASS inclusion/exclusion criteria outlined in Sections 5.3.1 and 5.3.2: 4 patients were either under 18 years old or have no age recorded; 64 patients were diagnosed with UC before July 2018 and are treatment-naïve; 9 patients did not have a UC diagnosis; 72 patients whose treatment commenced prior to 2018 and who have not started any additional treatments after July 2018 and 1 patient was treated exclusively with non-Tofacitinib JAK inhibitor. Therefore, 1,007 patients were included in the analysis for this progress report.

Figure 1 provides an overview of patients that have been enrolled in the PASS since the submission of the interim report to EMA in August 2024. As the figure shows, there has been a rapid increase in the study sample size due to intense efforts to obtain consent for data access for as many patients as possible within the UR-CARE system. The majority (45.8%) of the newly enrolled patients are from Spanish sites that are part of the Spanish ENEIDA registry (Table 3). The remaining patients are from individual sites in Greece, Belgium, Slovenia, Lithuania, Romania, and Bulgaria.

A marked increase in monthly patient recruitment was observed between January and March 2025. This peak is primarily explained by the fact that all participating Spanish centers received authorization to enroll patients during the same period. Consequently, the 15 Spanish sites simultaneously included all eligible patients who met the study's inclusion criteria. In addition, all Spanish patients originated from the national EINEDA database. Because EINEDA is synchronised with the URCARE database, the core patient information was already available at the time of site activation. Only study-specific variables required further completion by the investigators, which substantially facilitated the identification and rapid enrolment of eligible participants. This contrasts with non-Spanish centers, where patient inclusion follows the regular flow of visits with treating physicians, resulting in a more progressive recruitment pattern. Although this peak appears prominently in the recruitment curve, it does not indicate that recruitment subsequently stopped or slowed down. Instead, recruitment returned to a more stable and realistic rate aligned with routine clinical practice. The post-peak period reflects a normalised and sustainable recruitment dynamic rather than a decline in site activity.

Figure 1. Patients enrolled by month



Additionally, the total number of patients enrolled by country/site and study Cohort are provided in Table 3. Per Cohort, 216 patients are included in Cohort 1 (Tofacitinib), 956 in Cohort 2 (Biologics with/without concurrent immunosuppressants), 155 in Cohort 3 (Immunosuppressants only), and 463 in Cohort 4 (Naïve). Please note that some patients may belong to more than one Cohort. For example, patients who initiate more than one immunosuppressant or biological treatment could have multiple index dates defined if they meet the eligibility criteria, or a naïve patient who later starts a new treatment (for further details, refer to the Protocol or SAP document).

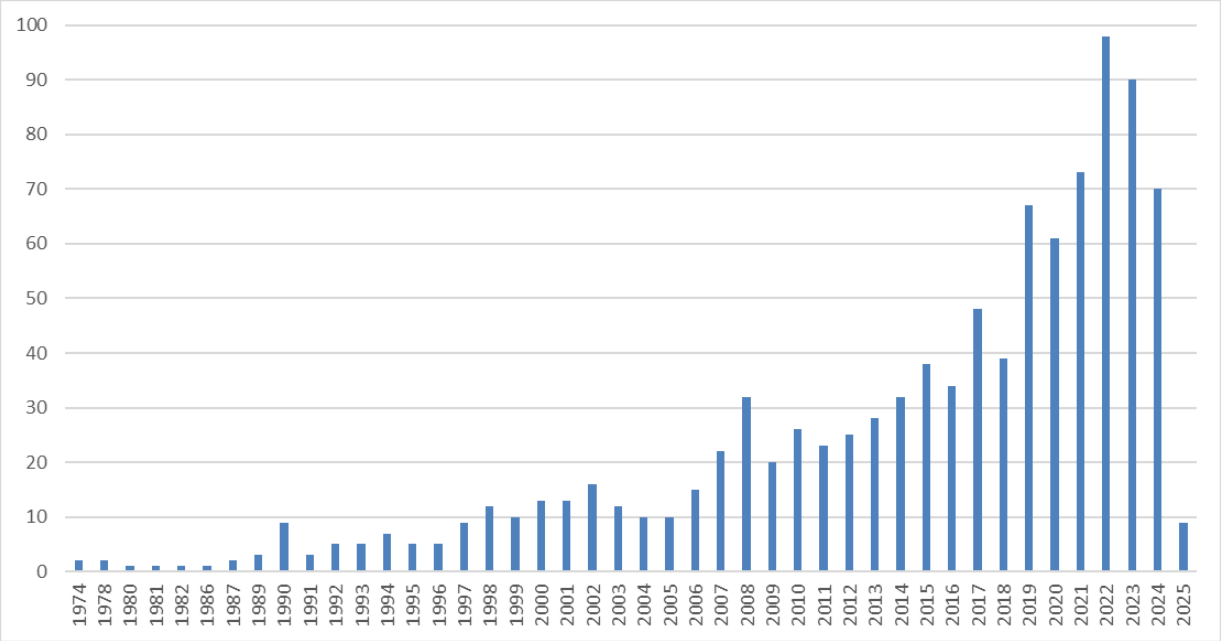
Table 3. Patients by country/site and study Cohort

Country/Site	Enrolled	Excluded	Analyzed	C1	C2	C3	C4
Spain	**497**	**36**	**461**	**136**	**439**	**92**	**200**
Hospital Clinic	22	11	11	4	11	1	4
Hospital Clínico Univ de Santiago de Compostela	89	3	86	16	84	12	49
Hospital Clínico Universitario Lozano Blesa	79	2	77	16	77	5	31
Hospital de Sant Joan Despí Moisès Broggi	30	1	29	18	33	10	11
Hospital General de Castellón	17	6	11	5	7	1	5
Hospital General Universitario de Valencia	1	1	1	1	1	0	0
Hospital La Princesa	27	0	27	12	34	8	5
Hospital Universitario Central de Asturias	40	0	39	7	40	8	15
Hospital Universitario de Burgos	91	2	89	23	64	24	44
Hospital Universitario de Cabueñes	4	1	3	2	3	0	1
Hospital Universitario de Canarias	40	5	35	14	34	10	11
Hospital Universitario Infanta Leonor	21	1	20	3	19	5	8
Hospital Universitario Marqués de Valdecilla	1	1	0	0	0	0	0
Hospital Universitario Río Hortega	35	2	33	15	32	8	16
Greece	**270**	**54**	**216**	**34**	**177**	**17**	**102**
GHA Evaggelismos-Ophthalmiatreion Athinon, Polykliniki	270	54	216	34	177	17	102
Belgium	**196**	**10**	**186**	**12**	**195**	**21**	**103**
AZ Delta	52	0	52	9	59	9	28
CHU Liège	36	7	29	3	32	0	19
Imelda Hospital	108	3	105	0	104	12	56
Slovenia	**131**	**34**	**97**	**17**	**96**	**2**	**40**
University Medical Centre of Ljubljana	131	34	97	17	96	2	40
Lithuania	**35**	**5**	**30**	**12**	**35**	**21**	**10**
Lithuanian university of health sciences	35	5	30	12	35	21	10
Romania	**23**	**8**	**15**	**4**	**13**	**2**	**6**
Colentina Clinical Hospital	23	8	15	4	13	2	6
Bulgaria	**5**	**3**	**2**	**1**	**1**	**0**	**2**
Acibadem City Clinic Tokuda Hospital	5	3	2	1	1	0	2
Total	**1157**	**150**	**1007**	**216**	**956**	**155**	**463**

C1 = Cohort 1 (Tofacitinib Cohort); C2 = CCohort 2 (biologics with/without concurrent immunosuppressants); C3 = CCohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort)

Figure 2 provides an overview of patients by year of UC diagnosis. Per the figure, the majority of patients (80.0%) were diagnosed between 2007 and 2024.

Figure 2. Patients by year of diagnosis



Patient enrollment by countries participating in the UR-CARE system are discussed further in the subsections below.

5.1.1. France

At the cutoff date of the progress report, no patient was included as no French site was participating in the PASS.

5.1.2. Belgium

At the cut-off date of the progress report, 196 patients were accessible in the study database. Of these, 10 patients were excluded from the analysis. Therefore, 186 patients (94.9%) were analyzed.

5.1.3. Bulgaria

At the cut-off date of the progress report, 5 patients were accessible in the study database. Of these, 3 patients were excluded from the analysis. Therefore, 2 patients (40.0%) were analyzed.

5.1.4. Lithuania

This country was not originally listed among the countries expected to participate in the PASS during protocol development. However, it is included in this report as one site from that country consented to participate due to the ongoing PASS promotion activities.

At the cut-off date of the progress report, 35 patients were accessible in the study database. Of them, 5 patients were excluded from the analysis. Therefore, 30 patients (85.7%) were analyzed.

5.1.5. Spain

At the cut-off date of the progress report, 497 patients were accessible in the study database. Of them, 36 patients were excluded from the analysis. Therefore, 461 were analyzed (92.8%).

5.1.6. The Netherlands

At the cut-off date of the progress report, no patients were included from this country as the contacted sites did not respond to the invitation to participate.

5.1.7. Greece

At the cut-off date of the progress report, 270 patients were accessible in the study database. Of them, 54 patients were excluded from the analysis. Therefore, 216 were analyzed (80.0%).

5.1.8. Poland

At the cut-off date of the progress report, no patients were included. The contacted sites either did not respond to the invitation to participate or lacked sufficient staff availability to complete the prospective module required for the PASS.

5.1.9. Slovenia

At the cut-off date of the progress report, 131 patients were accessible in the study database. Of them, 34 patients were excluded from the analysis. Therefore, 97 were analyzed (74.0%).

5.1.10. Croatia

At the cut-off date of the progress report, no patients were included. The contacted sites either did not respond to the invitation to participate or lacked sufficient staff availability to complete the prospective module required for the PASS.

5.1.11. Romania

At the cut-off date of the progress report, 23 patients were accessible in the study database. Of them, 8 patients were excluded from the analysis. Therefore, 15 were analyzed (65.2%).

5.1.12. United Kingdom

At the cut-off date of the progress report, no patients were included from this country. Only one site expressed interest in participating in the study; however, it was not registered in the UR-CARE database. The administrative procedures required for registration were considered too burdensome by the site, and the site ultimately decided not to participate in the study.

5.2. Study Conduct

For this progress report, data cut off was 29 September 2025.

5.2.1. Data entered by form

As described in the protocol (Appendix 1. Protocol), for each research study that uses the UR-CARE platform, a prospective module is developed which is specific to that research study. This prospective module is used to collect study-specific variables. Data in the prospective module are entered into the UR-CARE system by individual sites via online forms. The contents of the various URCARE and study-specific forms are summarized below. Each form is used to collect baseline disease-related information, treatment related information as well as key study specific variables such as inclusion criteria and safety events of interest. Table 4-Table 6 show the number of patients missing in each form.

UR-CARE Forms	**Contents**
Patient info	patients' demographic data (age, sex, race, country of birth, and their vital status at the end of the study).
Disease	Information related to the diagnosis of ulcerative colitis, such as the date of diagnosis, location, or complications.
Endoscopy	Information regarding disease severity (Mayo score, UCEIS score).
Imaging	Any imaging tests performed on the patient during follow-up.
Follow-up & Laboratory Tests	Data from follow-up visits or laboratory tests carried out during follow-up.
Conventional treatment	Information about conventional treatments used by patients during follow-up. This form does not necessarily need to be completed for all patients, as some may not have received the conventional treatment.
Immunomodulators	Information about Immunomodulators treatments used by patients during follow-up. This form does not necessarily need to be completed for all patients, as some may not have received the Immunomodulators treatment.
Biologics	Information about Biologics treatments used by patients during follow-up. This form does not necessarily need to be completed for all patients, as some may not have received the Biologics treatment.
Comorbidities	Information on infections, solid neoplasms, hematologic neoplasms, or other comorbidities.
Screening for infections	Information about the patient's vaccination status.
Study specific forms	**Contents**
Inclusion criteria	Data related to the patient's inclusion in the study
Risk factors (evaluation of VTE)	Information on VTE risk factors
Other treatments	Information about other treatments received
IBD treatment change	Information on patients who have changes in their IBD treatment
Tofacitinib	Information about treatment with Tofacitinib
Key Safety Event of Interest	Information regarding patient safety throughout the study

Overall, both the “Patient Info” and “Disease” forms have been included. It should be noted that the “Endoscopy” form, which assesses disease severity using the Mayo score, is incomplete for all patients in Spain and for the majority of patients in other countries. The “Imaging” form is also largely incomplete, which may be attributable to the fact that imaging procedures are not routinely performed in standard clinical practice for these patients. Additionally, there is a considerable amount of missing data in follow-up visits and laboratory tests; however, these variables are not critical for the conduct of the PASS TOFA study. Conversely, the treatment-related forms (“Immunomodulators” and “Biologics”) appear to be consistently completed across all participating countries. Regarding the “Comorbidities” and “Screening for infections” forms, completion rates should be improved, particularly in countries other than Spain.

Table 4. Missing data by UR-CARE form – Enrolled population

Country/Site		Patient info	Disease	Endoscopy	Imaging	Follow-up & Laboratory Tests	Conventional treatment	Immunomodulators*	Biologics*	Comorbidities	Screening for infections
	N enrolled	N missing									
Spain	**497**	**0**	**0**	**497**	**497**	**497**	**18**	**236**	**138**	**76**	**129**
Hosp. Clinic	22	0	0	22	22	22	1	10	8	1	18
Hosp. Univ. Santiago de Compostela	89	0	0	89	89	89	1	54	36	5	59
Hosp. Clínico Univ. Lozano Blesa	79	0	0	79	79	79	0	51	15	0	3
Hosp. Sant Joan Despí Moisès Broggi	30	0	0	30	30	30	0	5	1	0	0
Hosp. Gen Castellón	17	0	0	17	17	17	0	9	7	9	8
Hosp. Gen Univ. Valencia	1	0	0	1	1	1	0	0	0	0	0
Hosp. La Princesa	27	0	0	27	27	27	1	7	2	1	9
Hosp. Univ. Central de Asturias	40	0	0	40	40	40	0	16	9	0	0
Hosp. Univ. de Burgos	91	0	0	91	91	91	3	33	33	30	2
Hosp. Univ. de Cabueñes	4	0	0	4	4	4	0	1	1	0	3
Hosp. Univ. de Canarias	40	0	0	40	40	40	12	17	8	26	19
Hosp. Univ. Infanta Leonor	21	0	0	21	21	21	0	11	6	0	0
Hosp. Univ. Marqués de Valdecilla	1	0	0	1	1	1	0	1	1	1	0
Hosp. Univ. Río Hortega	35	0	0	35	35	35	0	21	11	3	8
Greece	**270**	**0**	**0**	**235**	**267**	**267**	**69**	**210**	**85**	**251**	**266**
GHA	270	0	0	235	267	267	69	210	85	251	266
Belgium	**196**	**0**	**1**	**188**	**196**	**157**	**31**	**115**	**39**	**96**	**194**
AZ Delta	52	0	0	52	52	13	15	26	5	34	51
CHU Liège	36	0	1	29	36	36	16	28	9	35	36
Imelda Hospital	108	0	0	107	108	108	0	61	25	27	107
Slovenia	**131**	**0**	**0**	**62**	**131**	**0**	**0**	**121**	**37**	**129**	**31**
Univ Medical Centre of Ljubljana	131	0	0	62	131	0	0	121	37	129	31
Lithuania	**35**	**0**	**0**	**0**	**32**	**4**	**0**	**9**	**10**	**31**	**33**
Lithuanian univ of health sciences	35	0	0	0	32	4	0	9	10	31	33
Romania	**23**	**0**	**0**	**1**	**21**	**2**	**2**	**21**	**10**	**13**	**7**
Colentina Clinical Hospital	23	0	0	1	21	2	2	21	10	13	7
Bulgaria	**5**	**0**	**0**	**1**	**4**	**4**	**1**	**4**	**4**	**4**	**2**
Acibadem City Clinic Tokuda Hosp	5	0	0	1	4	4	1	4	4	4	2
Total, (%)	**1157**	**0 (0.0%)**	**1 (0.1%)**	**984 (85.0%)**	**1148 (99.2%)**	**931 (80.5%)**	**121 (10.5%)**	**716 (61.9%)**	**323 (27.9%)**	**600 (51.9%)**	**662 (57.2%)**

* These forms do not necessarily need to be completed for all patients, as some may not have received the specific treatment for each form.

There are 93 patients (8.0%) who did not complete the “Inclusion Criteria” form and were therefore automatically excluded from the analysis population (Table 5). It is recommended that this form be completed for all patients in order to improve the recruitment of analyzable cases. The “Risk factors (evaluation of VTE)” and “Other treatments” forms are missing for approximately one-third of the sample; thus, their completion should be prioritized whenever possible. The “IBD treatment change,” “Tofacitinib,” and “Key Safety Event of Interest” forms should be closely monitored to ensure they are completed in cases where treatment changes occur, Tofacitinib is administered, or an adverse event of interest arises, respectively.

Table 5. Missing data by prospective PASS module form – Enrolled population

Country/Site	N	Inclusion criteria	Risk factors (evaluation of VTE)	Other treatments	IBD treatment change*	Tofacitinib**	Key Safety event of Interest ***
	N enrolled	N missing					
Spain	**497**	**86**	**168**	**172**	**392**	**180**	**428**
Hosp. Clinic	22	0	14	14	22	14	22
Hosp. Univ. Santiago de Compostela	89	0	0	1	62	4	89
Hosp. Clínico Univ. Lozano Blesa	79	0	18	18	59	20	50
Hosp. Sant Joan Despí Moisès Broggi	30	0	14	15	16	9	25
Hosp. Gen Castellón	17	15	16	16	17	16	17
Hosp. Gen Univ. Valencia	1	0	1	1	1	1	1
Hosp. La Princesa	27	0	1	1	22	2	26
Hosp. Univ. Central de Asturias	40	0	0	0	28	0	13
Hosp. Univ. de Burgos	91	71	72	73	87	72	91
Hosp. Univ. de Cabueñes	4	0	0	0	0	0	4
Hosp. Univ. de Canarias	40	0	4	5	31	19	37
Hosp. Univ. Infanta Leonor	21	0	1	1	13	1	17
Hosp. Univ. Marqués de Valdecilla	1	0	1	1	1	1	1
Hosp. Univ. Río Hortega	35	0	26	26	33	21	35
Greece	**270**	**6**	**28**	**43**	**216**	**73**	**268**
GHA	270	6	28	43	216	73	268
Belgium	**196**	**0**	**16**	**16**	**157**	**86**	**178**
AZ Delta	52	0	16	16	42	3	42
CHU Liège	36	0	0	0	35	2	36
Imelda Hospital	108	0	0	0	80	81	100
Slovenia	**131**	**0**	**13**	**13**	**129**	**13**	**131**
Univ Medical Centre of Ljubljana	131	0	13	13	129	13	131
Lithuania	**35**	**0**	**6**	**11**	**25**	**6**	**35**
Lithuanian univ of health sciences	35	0	6	11	25	6	35
Romania	**23**	**0**	**23**	**23**	**23**	**22**	**23**
Colentina Clinical Hospital	23	0	23	23	23	22	23
Bulgaria	**5**	**1**	**4**	**4**	**5**	**4**	**5**
Acibadem City Clinic Tokuda Hosp	5	1	4	4	5	4	5
Total, (%)	**1157**	**93 (8.0%)**	**258 (22.3%)**	**282 (24.4%)**	**947 (81.8%)**	**384 (33.2%)**	**1068 (92.3%)**

*One form in each treatment change. These data might not be missing but rather indicates that the patients have not experienced any changes in their treatments.
** This form indicates whether the patient takes Tofacitinib (Yes or No).
***These data might not be missing but rather indicate that the patients have not experienced any Key Safety Events of Interest.

5.2.2. Patient baseline characteristics

Data was available for nearly all patients on demographic and disease characteristics, with relatively low proportions of missing data for smoking and family history of IBD (Table 6). , data was missing higher proportions of patients for the Mayo score (missing in 338 patients, 33.6%), comorbidities (missing in 600 patients, 59.6%), and VTE risk factors (missing in 258 patients, 25.6%).

Table 6. Missing baseline data – Analyzed population

Country/Site	N	Demographic data	Smoking	Disease characteristics	Total/Partial Mayo Score	Family history of IBD	Comorbidities	VTE risk
	N analyzed	N missing						
Spain	**461**	**0**	**30**	**0**	**170**	**36**	**76**	**168**
Hosp. Clinic	11	0	0	0	5	0	1	14
Hosp. Univ. Santiago de Compostela	86	0	9	0	3	15	5	0
Hosp. Clínico Univ. Lozano Blesa	77	0	0	0	5	2	0	18
Hosp. Sant Joan Despí Moisès Broggi	29	0	0	0	11	0	0	14
Hosp. Gen Castellón	11	0	6	0	8	6	9	16
Hosp. Gen Univ. Valencia	1	0	0	0	1	0	0	1
Hosp. La Princesa	27	0	2	0	6	1	1	1
Hosp. Univ. Central de Asturias	39	0	0	0	38	0	0	0
Hosp. Univ. de Burgos	89	0	2	0	63	3	30	72
Hosp. Univ. de Cabueñes	3	0	0	0	0	0	0	0
Hosp. Univ. de Canarias	35	0	3	0	2	3	26	4
Hosp. Univ. Infanta Leonor	20	0	0	0	1	0	0	1
Hosp. Univ. Río Hortega	33	0	8	0	27	6	3	26
Greece	**216**	**2**	**6**	**1**	**3**	**11**	**251**	**28**
GHA	216	2	6	1	3	11	251	28
Belgium	**186**	**0**	**14**	**0**	**150**	**26**	**96**	**16**
AZ Delta	52	0	1	0	52	3	34	16
CHU Liège	29	0	0	0	0	0	35	0
Imelda Hospital	105	0	13	0	98	23	27	0
Slovenia	**97**	**0**	**0**	**0**	**14**	**0**	**129**	**13**
Univ Medical Centre of Ljubljana	97	0	0	0	14	0	129	13
Lithuania	**30**	**0**	**2**	**0**	**1**	**0**	**31**	**6**
Lithuanian univ of health sciences	30	0	2	0	1	0	31	6
Romania	**15**	**0**	**7**	**0**	**0**	**9**	**13**	**23**
Colentina Clinical Hospital	15	0	7	0	0	9	13	23
Bulgaria	**2**	**0**	**0**	**0**	**0**	**0**	**4**	**4**
Acibadem City Clinic Tokuda Hosp	2	0	0	0	0	0	4	4
Total, (%)	**1007**	**2 (0.2%)**	**59 (5.9%)**	**1 (0.1%)**	**338 (33.6%)**	**82 (8.1%)**	**600 (59.6%)**	**258 (25.6%)**

5.2.3. Drug exposure

In general, there is a considerable amount of missing data on drug exposure particularly regarding treatment end dates, which are essential for accurately classifying patients into Cohorts. Country-specific data is presented below. Therefore, we believe it is necessary to improve data collection in this area. Additionally, some treatment dates appear to be incorrect,

as there are instances of simultaneous treatments that should not be possible. If improving data quality is not feasible, we propose imputing the end date of a treatment as the start date of the subsequent treatment at the time of the analysis for the final report.

5.2.3.1. Spain

In Spain, there were 136 patients exposed to Tofacitinib, with an average exposure of 1.9 years; 439 patients were exposed to biologics, with an average exposure of 1.7 years; and 92 patients were exposed to immunosuppressants, with an average exposure of 1.2 years. There were 200 patients who were naïve for an average of 2.4 years (Table 7).

Table 7. Drug exposure - Spain – Analyzed population

Country	C1		C2		C3		C4	
	N	Years	N	Years	N	Years	N	Years
Spain	**136**	**1.9**	**439**	**1.7**	**92**	**1.2**	**200**	**2.4**
Tofacitinib	**136**	**1.9**						
Tofacitinib	136	1.9	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Biologics	**NA**	**NA**	**439**	**1.7**	**NA**	**NA**	**NA**	**NA**
Adalimumab/Biosimilars			52	1.6				
Adalimumab/Biosimilars+Azathioprine			16	1.9				
Adalimumab/Biosimilars+Mercaptopurine			2	2.1				
Adalimumab/Humira			13	0.5				
Adalimumab/Humira+Azathioprine			4	3.1				
Azathioprine+Infliximab/Biosimilars			2	2.1				
Certolizumab			1	0.1				
Golimumab			8	2.0				
Golimumab+Azathioprine			4	3.0				
Golimumab+Methotrexate			1	3.5				
Infliximab/Biosimilars			91	1.5				
Infliximab/Biosimilars+Azathioprine			51	2.0				
Infliximab/Biosimilars+Mercaptopurine			8	1.3				
Infliximab/Biosimilars+Methotrexate			4	4.0				
Infliximab/Remicade			6	0.6				
Infliximab/Remicade+Azathioprine			6	0.8				
Mercaptopurine+Infliximab/Biosimilars			1	0.3				
Mirikizumab			1	5.7				
Ustekinumab			49	1.6				
Ustekinumab/ Biosimilars			2	0.8				
Ustekinumab+Azathioprine			1	2.2				
Ustekinumab+Methotrexate			1	0.5				
Vedolizumab			98	1.9				
Vedolizumab+Azathioprine			12	3.0				
Vedolizumab+Mercaptopurine			1	3.2				
Vedolizumab+Methotrexate			3	2.0				
Vedolizumab+Tacrolimus			1	0.7				
Immunosuppressants	**NA**	**NA**	**NA**	**NA**	**92**	**1.2**	**NA**	**NA**
Anakinra+Ciclosporina					1	1.0		
Azathioprine					68	1.4		
Ciclosporin					6	0.1		
Mercaptopurine					9	1.2		
Methotrexate					5	0.5		
Tacrolimus					3	0.7		

C1 = CCohort 1 (Tofacitinib CCohort; C2 = CCohort 2 (biologics with/without concurrent immunosuppressants); C3 = CCohort 3 (immunosuppressants only); C4 = CCohort 4 (naive CCohort); NA = not applicable

5.2.3.2. Greece

In Greece, 34 patients were exposed to Tofacitinib, with an average exposure of 2.4 years; 177 patients were exposed to biologics, with an average exposure of 2.1 years; and 17 patients were exposed to immunosuppressants, with an average exposure of 1.5 years. There were 102 patients who were naïve for an average of 2.0 years (Table 8).

Table 8. Drug exposure - Greece – Analyzed population

Country	C1		C2		C3		C4	
	N	Years	N	Years	N	Years	N	Years
Greece	**34**	**2.4**	**177**	**2.1**	**17**	**1.5**	**102**	**2.0**
Tofacitinib	**34**	**2.4**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Tofacitinib	34	2.4						
Biologics	**NA**	**NA**	**177**	**2.1**	**NA**	**NA**	**NA**	**NA**
Adalimumab/Biosimilars			6	1.8				
Adalimumab/Humira			16	2.7				
Azathioprine+Infliximab/Remicade			1	1.7				
Golimumab			3	3.9				
Infliximab/Biosimilars			44	1.5				
Infliximab/Biosimilars+Azathioprine			3	4.6				
Infliximab/Remicade			22	1.6				
Infliximab/Remicade+Azathioprine			5	2.9				
Lutikizumab			1	0.4				
Methotrexate+Infliximab/Remicade			2	2.9				
Risankizumab			1	2.7				
Ustekinumab			13	1.7				
Vedolizumab			58	2.3				
Vedolizumab+Azathioprine			2	1.7				
Immunosuppressants	**NA**	**NA**	**NA**	**NA**	**17**	**1.5**	**NA**	**NA**
Azathioprine					10	1.9		
Methotrexate					1	1.4		
Ozanimod					6	0.9		

C1 = Cohort 1 (Tofacitinib Cohort; C2 = Cohort 2 (biologics with/without concurrent immunosuppressants); C3 = Cohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort); NA = not applicable

5.2.3.3. Belgium

In Belgium, 12 patients were exposed to Tofacitinib with an average exposure of 3.5 years; 195 patients were exposed to biologics with an average exposure of 2.2 years; and 21 patients were exposed to immunosuppressants, with an average exposure of 1.0 year. There were 103 patients who were naïve for an average of 1.9 years (Table 9)

Table 9. Drug exposure - Belgium – Analyzed population

Country	C1		C2		C3		C4	
	N	Years	N	Years	N	Years	N	Years
Belgium	**12**	**3.5**	**195**	**2.2**	**21**	**1.0**	**103**	**1.9**
Tofacitinib	**12**	**3.5**	NA	NA	NA	NA	NA	NA
Tofacitinib	12	3.5	NA	NA	NA	NA	NA	NA
Biologics			**195**	**2.2**	**NA**	**NA**	**NA**	**NA**
Adalimumab/Biosimilars			9	2.2				
Adalimumab/Biosimilars+Azathioprine			1	1.8				
Adalimumab/Humira			4	2.5				
Azathioprine+Infliximab/Biosimilars			2	5.7				
Golimumab			2	0.1				
Infliximab/Biosimilars			19	1.8				
Infliximab/Biosimilars+Azathioprine			12	2.1				
Infliximab/Biosimilars+Mercaptopurine			13	4.4				
Infliximab/Biosimilars+Methotrexate			8	3.3				
Infliximab/Remicade			1	0.4				
Mercaptopurine+Infliximab/Biosimilars			1	1.8				
Mirikizumab			9	0.7				
Risankizumab			1	3.5				
Ustekinumab			13	1.6				
Vedolizumab			98	2.0				
Vedolizumab+Azathioprine			1	2.1				
Vedolizumab+Methotrexate			1	6.5				
Immunosuppressants	**NA**	**NA**	**NA**	NA	**21**	**1.0**	**NA**	**NA**
Azathioprine					6	1.3		
Etrasimod					6	0.6		
Mercaptopurine					6	0.2		
Methotrexate					1	0.7		
Ozanimod					1	5.0		
Rituximab					1	3.3		

C1 = Cohort 1 (Tofacitinib Cohort; C2 = Cohort 2 (biologics with/without concurrent immunosuppressants); C3 = Cohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort); NA = not applicable

5.2.3.4. Slovenia

In Slovenia, 17 patients were exposed to Tofacitinib with an average exposure of 2.5 years; 96 patients were exposed to biologics with an average exposure of 2.2 years; and 2 patients were exposed to immunosuppressants with an average exposure of 1.0 year. There were 40 patients who were naïve for an average of 1.6 years (Table 10).

Table 10. Drug exposure - Slovenia – Analyzed population

Country	**C1**		**C2**		**C3**		**C4**	
	N	**Years**	**N**	**Years**	**N**	**Years**	**N**	**Years**
Slovenia	**17**	**2.5**	**96**	**2.2**	**2**	**1.0**	40	1.6
Tofacitinib	**17**	**2.5**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Tofacitinib	17	2.5						
Biologics	**NA**	**NA**	**96**	**2.2**	**NA**	**NA**	**NA**	**NA**
Adalimumab/Biosimilars			4	3.1				
Adalimumab/Humira			1	4.9				
Golimumab			3	0.4				
Infliximab/Biosimilars			27	1.4				
Mirikizumab			6	0.5				
Ustekinumab			12	2.5				
Vedolizumab			43	2.8				
Immunosuppressants	**NA**	**NA**	**NA**	**NA**	**2**	**1.0**	**NA**	**NA**
Azathioprine					1	1.5		
Methotrexate					1	0.5		

C1 = Cohort 1 (Tofacitinib Cohort; C2 = Cohort 2 (biologics with/without concurrent immunosuppressants); C3 = Cohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort); NA = not applicable

5.2.3.5. Lithuania

In Lithuania, 12 patients were exposed to Tofacitinib with an average exposure of 1.5 years; 35 patients were exposed to biologics with an average exposure of 1.6 years; and 21 patients were exposed to immunosuppressants with an average exposure of 0.6 years. There were 10 patients who were naïve for an average of 1.9 years (Table 11).

Table 11. Drug exposure - Lithuania – Analyzed population

Country	C1		C2		C3		C4	
	N	Years	N	Years	N	Years	N	Years
Lithuania	**12**	**1.5**	**35**	**1.6**	**21**	**0.6**	**10**	**1.9**
Tofacitinib	**12**	**1.5**	NA	NA	NA	NA	NA	NA
Tofacitinib	12	1.5	NA	NA	NA	NA	NA	NA
Biologics	**NA**	**NA**	**35**	**1.6**	**NA**	**NA**	**NA**	**NA**
Adalimumab/Biosimilars+Azathioprine			2	0.0				
Adalimumab/Humira			5	2.7				
Adalimumab/Humira+Azathioprine			4	1.5				
Infliximab/Biosimilars			1	0.2				
Infliximab/Remicade			2	1.2				
Infliximab/Remicade+Azathioprine			4	3.5				
Risankizumab			2	1.3				
Ustekinumab			5	1.8				
Ustekinumab+Azathioprine			2	1.1				
Vedolizumab			7	0.7				
Vedolizumab+Azathioprine			1	1.0				
Immunosuppressants	NA	NA	NA	NA	**21**	**0.6**	NA	NA
Azathioprine					17	0.7		
Ciclosporin					4	0.1		

C1 = Cohort 1 (Tofacitinib Cohort; C2 = Cohort 2 (biologics with/without concurrent immunosuppressants); C3 = Cohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort); NA = not applicable

5.2.3.6. Romania

In Romania, 4 patients were exposed to Tofacitinib with an average exposure of 3.1 years; 13 patients were exposed to biologics with an average exposure of 1.6 years; and 2 patients were exposed to immunosuppressants with an average exposure of 1.8 years. There were 6 patients who were naïve for an average of 2.1 years (Table 12).

Table 12. Drug exposure - Romania– Analyzed population

Country	C1		C2		C3		C4	
	N	Years	N	Years	N	Years	N	Years
Romania	**4**	**3.1**	**13**	**1.6**	**2**	**1.8**	**6**	**2.1**
Tofacitinib	**4**	**3.1**	NA	NA	NA	NA	NA	NA
Tofacitinib	4	3.1						
Biologics	**NA**	**NA**	**13**	**1.6**	**NA**	**NA**	**NA**	**NA**
Adalimumab/Biosimilars			3	2.2				
Infliximab/Biosimilars			4	1.6				
Ustekinumab			1	0.3				
Vedolizumab			5	1.7				
Immunosuppressants	**NA**	**NA**	**NA**	**NA**	**2**	**1.8**	**NA**	**NA**
Azathioprine					2	1.8		

C1 = Cohort 1 (Tofacitinib Cohort; C2 = Cohort 2 (biologics with/without concurrent immunosuppressants); C3 = Cohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort); NA = not applicable

5.2.3.7. Bulgaria

In Bulgaria, 1 patient was exposed to Tofacitinib with exposure of 4.8 years; 1 patient was exposed to biologics with exposure of 0.4 years. No patients were exposed to immunosuppressants. There were 2 patients who were naïve for an average of 2.9 years (Table 13).

Table 13. Drug exposure - Bulgaria – Analyzed population

Country	C1		C2		C3		C4	
	N	Years	N	Years	N	Years	N	Years
Bulgaria	**1**	**4.8**	**1**	**0.4**	NA	NA	**2**	**2.9**
Tofacitinib	**1**	**4.8**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Tofacitinib	1	4.8						
Biologics	**NA**	**NA**	**1**	**0.4**	**NA**	**NA**	**NA**	**NA**
Infliximab/Biosimilars			1	0.4				

C1 = Cohort 1 (Tofacitinib Cohort; C2 = Cohort 2 (biologics with/without concurrent immunosuppressants); C3 = Cohort 3 (immunosuppressants only); C4 = Cohort 4 (naive Cohort); NA = not applicable

5.2.4. Safety endpoints of interest

Table 14 shows the total number of safety events reported by the participating sites as of the data cut off date, regardless of treatment status. Notably, despite the large sample size and the fact that data collection spanned a pandemic period, no deaths were reported. It is possible that deceased patients who were treated during the study period are not being adequately captured within UR-CARE.

The most commonly reported event was infection (109 events), followed by pregnancies (43 events) and safety events classified as "other" (46 events). Malignancies excluding NMSC accounted for 6 cases, with 1 additional case of NMSC. No cases of lung cancer, lymphoma (Hodgkin's or non-Hodgkin's), or chronic lymphocytic lymphoma were reported. Two MACE were observed, with no myocardial infarctions. One VTE was reported. No cases of progressive multifocal leukoencephalopathy (PML), gastrointestinal perforations, or herpes zoster were observed. Additionally, 8 fracture events were recorded. No all-cause mortality events were reported.

Table 14. Events reported by endpoint – Analyzed population

Endpoint	Number of events reported	Number of valid events
Malignancy excluding NMSC	6	5
VTE (DVT or PE)	1	1
NMSC	1	1
Lung cancer	0	0
Lymphoma	0	0
Hodgkin's lymphoma	0	0
Non-Hodgkin's lymphoma	0	0
Chronic lymphocytic lymphoma	0	0
Infections	109	86
Opportunistic infections	4	4
Herpes Zoster	0	0
MACE	2	2
MI	0	0
PML	0	0
GI perforations	0	0
Fractures	8	5
All-cause mortality	0	0
Pregnancies	43	1
Other	46	26

NMSC, Non-melanoma skin cancer; VTE, Venous Thromboembolism; DVT, Deep Vein Thrombosis; PE, Pulmonary embolism; MACE, Major adverse cardiovascular events; MI, myocardial infarction; PML, Progressive Multifocal Leukoencephalopathy; GI, Gastrointestinal

By country, sites in Spain contributed 84.8% of the total events, Belgium 14.1%, and Greece 1.1%. For the countries that reported zero events, note that each had fewer than 100 patients enrolled. By center, it seems that events are concentrated in certain centers (Hosp. Univ. Central de Asturias with the 43.8% of the total events and Hosp. Clínico Univ. Lozano Blesa with the 32.6%), with few events occurring in other centers of similar size (Table 15). There seems to be a difference in the reporting of adverse events by country/site, particularly in the reporting of infections.

Table 15. Events reported by endpoint by country and site – Analyzed population

Country/Site	N	Total Events*	Malignancy Non-NMSC	VTE	NMSC	Lung cancer	Lymphoma	Infections	Opportunistic Infections	Herpes Zoster	MACE	MI	PML	GI perforations	Bone fracture	All-cause mortality	Pregnancies	Other
Spain	461	**151**	**4**	**0**	**0**	**0**	**0**	**97**	**3**	**0**	**2**	**0**	**0**	**0**	**7**	**0**	**36**	**37**
Hosp. Clinic	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hosp. Univ. Santiago de Compostela	86	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hosp. Clínico Univ. Lozano Blesa	77	58	1	0	0	0	0	24	1	0	1	0	0	0	6	0	23	25
Hosp. Sant Joan Despí Moisès Broggi	29	7	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	3
Hosp. Gen Castellón	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hosp. Gen Univ. Valencia	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hosp. La Princesa	27	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Hosp. Univ. Central de Asturias	39	78	1	0	0	0	0	72	0	0	0	0	0	0	0	0	1	5
Hosp. Univ. de Burgos	89	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0
Hosp. Univ. de Cabueñes	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hosp. Univ. de Canarias	35	3	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
Hosp. Univ. Infanta Leonor	20	4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	3
Hosp. Univ. Marqués de Valdecilla	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hosp. Univ. Río Hortega	33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0
Greece	216	**2**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**1**
GHA	216	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1
Belgium	186	**25**	**1**	**1**	**1**	**0**	**0**	**12**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**8**
AZ Delta	52	11	0	0	1	0	0	5	0	0	0	0	0	0	1	0	0	4
CHU Liège	29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Imelda Hospital	105	14	1	1	0	0	0	7	1	0	0	0	0	0	0	0	0	4
Slovenia	97	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**0**
Univ Medical Centre of Ljubljana	97	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
Lithuania	30	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	2	**0**
Lithuanian univ of health sciences	30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
Romania	15	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**
Colentina Clinical Hospital	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Bulgaria	2	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Acibadem City Clinic Tokuda Hosp	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	1007	**178**	**6**	**1**	**1**	**0**	**0**	**109**	**4**	**0**	**2**	**0**	**0**	**0**	**8**	**0**	**43**	**46**

*Pregnancies are not included in total events.
NMSC, Non-melanoma skin cancer; VTE, Venous Thromboembolism; DVT, Deep Vein Thrombosis; PE, Pulmonary embolism; MACE, Major adverse cardiovascular events; MI, myocardial infarction; PML, Progressive Multifocal Leukoencephalopathy; GI, Gastrointestinal

5.3. Actions Taken For Safety Reasons

No such actions have been taken.

5.4. Overall Conclusions

5.4.1. Sample Size Challenges

The initiation of study A3921352 progressed more slowly than anticipated, primarily due to issues with site consent and data access within the UR-CARE registry, as well as the time required to obtain national and institutional approvals. These regulatory and administrative processes, which vary considerably between countries, resulted in delayed data access and limited patient enrollment during the initial phase.

Since early 2024, concerted efforts by the MAH, B-COM, and the UR-CARE Steering Committee have led to improved communication with participating centers and the reactivation of registration procedures that had been temporarily paused. As a result, patient inclusion has become more active, with several new centers, particularly in Spain, recently providing consent for data sharing.

To further strengthen recruitment and ensure the achievement of enrollment objectives by March 2026 (end of data collection), several additional actions are being implemented or planned:
• Continued targeted outreach to existing and potential UR-CARE sites to facilitate rapid engagement and consent.
• Dissemination of updated study information through periodic UR-CARE newsletters and investigator communications.
• Organization of short virtual orientation sessions to raise awareness of study objectives and simplify site participation procedures.
• Enhanced follow-up with participating sites to ensure timely data entry and completeness within the registry.

By the end of data collection for this study (i.e., 31 March 2026), the status of each patient will be finalized in the eCRF, including confirmation of their vital status in Form 1 (“Patient”). After this cut-off, no new adverse events (AEs/SAEs) or deaths occurring beyond this date will be recorded. However, ongoing data cleaning, consistency checks, and monitoring activities performed by the CRO may continue beyond this date to ensure full data verification for the final study report.

These combined measures are expected to sustain the current positive trend in enrollment and ensure the robustness of the final dataset for analysis by the planned completion date in March 2026.

As specified in the study protocol, a comparative analysis will be conducted only if at least 500 patients have been exposed to tofacitinib. If this threshold is not met, all analyses will remain purely descriptive. Based on the current sample size, the number of tofacitinib-exposed patients is sufficient to support a descriptive analysis but does not allow for a comparative assessment.

It should be noted that, at the time of the final study analysis, if the target of 500 tofacitinib-exposed patients has been reached, the planned comparative analysis will be performed accordingly. Otherwise, the reporting will remain descriptive in line with the predefined methodological framework.

5.4.2. Data Quality and Ongoing Data Verification

A considerable amount of missing data has been identified, particularly regarding treatment end dates, which are essential for accurate Cohort classification. This limitation primarily stems from the characteristics of the UR-CARE registry, a relatively young database established in 2018. To date, Study A3921352 is the first project to implement detailed, patient-level monitoring within UR-CARE; no prior studies or initiatives have yet focused on systematically improving or validating data quality in this registry.

Since UR-CARE operates on a voluntary data entry model, investigators are not required to complete specific fields, and the database currently lacks internal coherence checks or automated alerts to detect inconsistencies. As a result, data accuracy depends entirely on investigator engagement and willingness to provide complete and reliable information.

During data review, a number of inconsistencies were observed, including missing treatment end dates and instances of simultaneous treatments that should not occur clinically. To address these issues, it is considered necessary to strengthen data collection procedures, particularly for treatment timelines. Where correction through monitoring is not feasible, an imputation approach may be applied specifically, imputing a treatment end date as the start date of the subsequent treatment. Additionally, the creation of a predefined list of possible treatments is being considered to help identify and prevent errors such as the simultaneous use of contraindicated therapies.

During ongoing data review, it was also noted that baseline VTE risk factors are missing for a substantial proportion of patients across several participating countries. This issue concerns variables collected in the prospective PASS-specific module rather than the UR-CARE core module. Although continuous monitoring activities are already in place (including systematic tracking of missing data, regular follow-up with sites, and investigator support for data correction) completeness for these specific variables remains suboptimal.

To further strengthen data collection, the following additional measures are being implemented:

1. Targeted investigator reminders focusing on the completion of baseline VTE risk factors, as well as other missing data in the prospective module.

2. Inclusion of short guidance notes within the prospective module clarifying expectations and facilitating accurate data entry.

3. Reinforcement during investigator meetings on the importance of these variables.

4. A dedicated newsletter summarizing data completion priorities and recent improvements.

Moreover, several complementary data quality initiatives are being deployed:

- Ongoing communication with the sites (queries, completion of data, reminders for key points).
- Regular newsletters encouraging participating sites to review their data for accuracy
- Technical method: pop-up messages through the database with reminders of key variables for completion (ICF, Mayo score, VTE variables, etc.).
- Closer collaboration with the study statisticians to anticipate analytical constraints and ensure data consistency across countries.

The MAH's CRO (B-COM) continues to perform rigorous and ongoing patient-level data monitoring, working directly with each participating site to complete missing information and correct inconsistencies. Following each monitoring visit, a tracking table summarizing missing or inconsistent data is sent to the site, and monthly follow-up is conducted. The CRO provides continuous support to investigators for any questions related to data entry and encourages them by highlighting the progress made in data correction, which contributes to improving both their own patient database and the overall study data quality.

In addition, for sites presenting a high rate of screen failures, the CRO performs targeted follow-up actions to reinforce study compliance. These include reminders of the inclusion and exclusion criteria as well as the patient follow-up procedures. Teleconferences or virtual meetings are organized with these sites to review the study methodology and ensure consistent application of the protocol across all centers.

Given the recent acceleration in patient enrollment and the absence of automated validation mechanisms within UR-CARE, this remains a detailed and labor-intensive process. A time lag exists between the present progress report and the full integration of all corrections; however, data verification activities are ongoing and expected to be completed for the final study report. Patient enrollment is still ongoing and will continue until the end of data collection (March 2026).

5.4.3. Underestimation of Safety Events and Ongoing Mitigation Measures

An apparent underestimation of safety events of interest has been observed in the current dataset. Despite the growing sample size and data collection covering the pandemic period, no deaths have been reported in the entire dataset at the progress report cutoff date.

This observation may be partly explained by a structural limitation in the UR-CARE registry (which impacts the PASS study design): each patient must provide written informed consent before participation in the PASS. Consequently, patients who might have otherwise met the study inclusion criteria, but who are already deceased and are unable to provide informed consent for the PASS are thus excluded from the analyses. As a result, there is likely an underestimation of mortality in the PASS due to this partial capture of mortality data.

Variables impacted by this partial capture of mortality data include all-cause mortality as well as composite endpoints that include fatal outcomes, notably major adverse cardiovascular events (MACE), for which cardiovascular death is a component.

This limitation was identified during the preparation of the progress report. Following this identification, the MAH's vendor petitioned the UR-CARE steering committee for an exception to the policy, and they subsequently approved a protocol amendment on 30 January 2026 to allow the inclusion of deceased patients without prior informed consent, in compliance with applicable data protection regulations (GDPR). However, implementation of this amendment requires resubmission and approval by national ethics committees in all PASS participating countries. Given the timelines associated with these regulatory and ethical approvals (between six months to one year depending on the country), the amendment will not become effective in a reasonable timeframe to be implemented for the PASS.

As a result, Study A3921352 will not include data from patients who died before providing informed consent, and this limitation should be considered when interpreting mortality-related results.

To mitigate the risk of underreporting other safety events, the CRO (B-COM) has implemented an active data reinforcement plan. This includes regular and systematic communication with all UR-CARE centers participating in the PASS, through periodic email reminders emphasizing the importance of reporting all safety events, whether minor or major, and whether they occurred retrospectively or prospectively in relation to the patient's participation in the study. In addition, the CRO provides individualized feedback to sites to ensure that reported events are accurately recorded and updated in the database.

These ongoing measures aim to improve the completeness and reliability of safety event reporting and to minimize potential underestimation in the final dataset.

5.4.4. Summary

There were 1,186 IBD patients in the UR-CARE database of which this study team had consent to access data for 1,157 IBD patients. Of these 1,157 patients, 150 patients were excluded for not meeting the PASS inclusion/exclusion criteria. Therefore, 1,007 patients were included in the analysis. Per Cohort, 216 patients are included in Cohort 1 (Tofacitinib), 956 in Cohort 2 (Biologics with/without concurrent immunosuppressants), 155 in Cohort 3 (Immunosuppressants only), and 463 in Cohort 4 (Naïve).

Per the protocol, the study is a descriptive analysis, and a comparative analysis will be conducted pending sample size feasibility. With these current numbers, there is a sufficient sample size for a descriptive analysis so the main objectives can be assessed. 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.

There is a considerable amount of missing data, particularly regarding treatment end dates, which are essential for accurately classifying patients into Cohorts. Actions to improve data completeness are in development per section 5.4.2, above. Additionally, some treatment dates appear to be incorrect, as there are instances of simultaneous treatments that should not be possible. If improving data quality is not feasible, it is proposed to impute the end date of a treatment as the start date of the subsequent treatment. It is also considered necessary to create a list of possible treatments (if feasible) in order to rule out errors, such as the simultaneous use of two contraindicated therapies.

There also appears to be an underestimation of safety events of interest in the patients. Notably, despite the large sample size and the fact that data collection spanned a pandemic period, no deaths were reported. This is most likely due to the partial capture of mortality-related outcomes, resulting in an underestimation of mortality. As such, results from mortality-related outcomes, including all-cause mortality and composite endpoints such as major adverse cardiovascular events (MACE) in the final report for the PASS will have to be interpreted with caution.

Finally, additional monitoring will be conducted by the CRO to ensure that all sites complete patient vital status information by the end of the data collection period (31 March 2026).

In conclusion, data entry needs to be improved, with particular emphasis on recording treatment end dates as well as including safety events of interest.

6. 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.

Document Approval Record

Document Name:	A3921352_PROGRESS REPORT_16FEB2026
Document Title:	A3921352_PROGRESS REPORT_16FEB2026

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	18-Feb-2026 14:57:03	Manager Approval
De Bernardi, Barbara	23-Feb-2026 08:33:08	EUQPPV Approval