# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## PASS information

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| **Title** | An Active Surveillance, Post-Authorization Study to Assess Tofacitinib Utilization Patterns and to Characterize the Safety of Tofacitinib Use in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from a US Administrative Healthcare Claims Database |
| **Protocol number** | A3921347 |
| **Protocol version identifier** | 3.0 |
| **Date** | 30 September 2024 |
| **HMA-EMA Catalogues of RWD Studies number** | EUPAS36041 |
| **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<br>Boulevard de la Plaine 17<br>1050 Bruxelles<br>Belgium |
| **Joint PASS** | No |
| **Research question and objectives** | **<u>Research Question 1</u>:** |

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| | What are the utilization patterns of tofacitinib in the United States (US) with regard to on-label and off-label use?<br><br>**Objectives:**<br>○ To estimate the proportion of tofacitinib users who receive the drug for the approved indications during the study period<br>○ To describe the characteristics of patients who are prescribed tofacitinib for on-label, off-label and unknown indications in terms of the following:<br>▪ Demographics (e.g., age, sex);<br>▪ Comorbidities;<br>▪ Prior and concurrent medications;<br>▪ Prescribed daily dose and duration of tofacitinib therapy<br>○ To estimate the proportion of UC patients on 5 mg twice daily or 11 mg once daily and 10 mg twice daily or 22 mg once daily maintenance therapies<br>○ To estimate the proportion of non-UC patients on 10 mg twice daily or 22 mg once daily therapy<br>○ To estimate the proportion of patients with approved indications who have ≥1 thrombosis risk factors and are prescribed tofacitinib, overall and stratified by dose<br>○ To estimate the proportion of tumor necrosis factor inhibitor (TNFi)- |

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| | naïve UC patients prescribed tofacitinib pre and post 01 July 2019<br><br>**Research Question 2**:<br>What are the incidence rates of safety events of interest (described below) in adult ulcerative colitis (UC) patients treated with tofacitinib (including the immediate-release formulation [dosed as 5 mg and 10 mg twice daily] and the extended-release formulation [dosed as 11 mg and 22 mg once daily] ) in the course of routine clinical care?<br><br>**Primary Objective**:<br>To estimate the incidence rate of malignancy, excluding non-melanoma skin cancer (NMSC), among adult UC patients who initiate tofacitinib in the course of routine clinical care.<br><br>**Secondary Objective**:<br><br>To estimate the incidence rates of other safety events of interest, including (but not limited to): lung cancer, lymphoma, NMSC, opportunistic infections (e.g. tuberculosis), major adverse cardiac events (MACE), venous thromboembolism (deep venous thrombosis [DVT] and pulmonary embolism [PE]), myocardial infarction (MI), hepatic events, serious infections, herpes zoster (HZ reactivation), progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, interstitial lung disease (ILD), fractures, surgery for UC, and death in adult UC patients who initiate tofacitinib in the course of routine clinical care.<br><br>Incidence rates will be estimated among:<br><br>Cohort 1: UC patients initiating tofacitinib, overall and stratified by dose (5 mg twice |

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| | daily, 11 mg once daily, 10 mg twice daily, 22 mg once daily ) and prior biologic use.<br><br>For contextualization and risk characterization purposes, incidence rates will also be estimated among the following groups:<br><br>Cohort 2: UC patients who initiate biologics, with/without concurrent immunomodulators/immunosuppressants, overall and stratified by TNFi/non-TNFi use and number of previous biologic treatments<br><br>Cohort 3: UC patients who initiate immunomodulators/immunosuppressants without concurrent biologics<br><br>Cohort 4: UC patients naïve to both biologics and immunomodulators/ immunosuppressants |
| **Country of study** | United States |
| **Author** | Dominque Sighoko, PhD, MPH<br>66 Hudson Blvd E<br>New York, NY 10001, |

**Marketing Authorization Holder(s)**

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| | United Kingdom |

## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 6-MP | 6-mercaptopurine |
| ADR | Adverse Drug Reaction |
| AE | Adverse event |
| AZA | Azathioprine |
| CI | Confidence interval |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DD | Daily dose |
| DMARD | Disease modifying antirheumatic drug |
| DVT | Deep vein thrombosis |
| EMA | European Medicines Agency |
| EU | European Union |
| GEP | Good Epidemiological Practice |
| GI | Gastrointestinal |
| GPP | Guidelines for Good Pharmacoepidemiology Practices |
| HMA | Heads of Medicines Agencies |
| HR | Hazard ratio |
| Hx | History |
| HZ | Herpes zoster |
| IBD | Inflammatory bowel disease |
| ICD | International Classification of Diseases |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEA | International Epidemiological Association |
| IEC | Independent Ethics Committee |
| ILD | Interstitial lung disease |
| ISPE | International Society for Pharmacoepidemiology |
| IR | Incidence rate |
| IRB | Institutional Review Board |
| JAK | Janus kinase |
| MACE | Major adverse cardiovascular events |
| MI | Myocardial Infarction |
| MTX | Methotrexate |
| NDA | New Drug Application |
| NI | Non-interventional |
| NMSC | Non-melanoma skin cancer |
| NSAIDs | Non-steroidal anti-inflammatory drugs |

| Abbreviation | Definition |
|---|---|
| OI | Opportunistic infection |
| PASS | Post-Authorization Safety Study |
| pcJIA | Polyarticular-course juvenile idiopathic arthritis |
| PE | Pulmonary embolism |
| PML | Progressive multifocal leukoencephalopathy |
| PsA | Psoriatic arthritis |
| RA | Rheumatoid arthritis |
| RMP | Risk management plan |
| RWD | Real-world data |
| SAP | Statistical analysis plan |
| TB | Tuberculosis |
| TNFi | Tumor necrosis factor inhibitor |
| UC | Ulcerative colitis |
| US | United States |
| USPI | United States prescribing information |
| VTE | Venous thromboembolism |

## 3. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
| Dominique Sighoko, MPH, PhD | Epidemiologist | Safety Surveillance Research, Pfizer, Inc. | 66 Hudson Blvd E, New York, NY 10001, |
| Fenglong Xie, PhD | Research Scientist | University of Alabama at Birmingham | 802 FOT building, Birmingham, 35294 |
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## 4. ABSTRACT


- **Title**: An Active Surveillance, Post-Authorization Study to Assess Tofacitinib Utilization Patterns and to Characterize the Safety of Tofacitinib Use in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from a US Administrative Healthcare Claims Database

- **Version:** 3.0

- **Date:** 30 September 2024

- **Main author/affiliation**: Dominique Sighoko,MPH, PhD, Pfizer, Inc.

- **Rationale and background**: Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the United States (US) in May 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). In July 2019, the US prescribing information (USPI) was updated to note that tofacitinib should be prescribed for adult patients with moderate-to-severe UC who have had an inadequate response or who are intolerant to tumor necrosis factor inhibitors (TNFis). In December 2019, the extended-release formulation was also approved for UC patients at a dose of 11 mg once daily and 22 mg once daily. Tofacitinib is also currently approved for adult patients with moderate-to-severe rheumatoid arthritis (RA) and active psoriatic arthritis (PsA) at a dose of 5 mg twice daily and 11 mg once daily, as well as at a dose of 5 mg twice daily for patients aged ≥2 years with active polyarticular course juvenile idiopathic arthritis (pcJIA). Due to the potential for off-label use of the 10 mg twice daily and 22 mg once daily dosing regimens in non-UC patients, as well as the potential for use of tofacitinib in non-indicated populations, it would be useful to understand the patterns of post approval use in the US.

  In addition, understanding of long-term safety associated with real-world tofacitinib use, including the potential risk of malignancy and other safety events of interest, is needed. Follow-up of large cohorts of patients over a long period can help in the evaluation of any potential risk of malignancy, as well as any other potential safety events of interest, that may be associated with tofacitinib treatment.

  To understand the patterns of tofacitinib use in the US, as well as to characterize the risk of safety events of interest that may be associated with its use, Pfizer will implement a post-approval, drug utilization and active surveillance study using a United States (US) administrative healthcare claims database. This non-interventional study is a post-marketing commitment to the US Food and Drug Administration (FDA), and is also designated as a category 3 study in the European Union (EU) risk management plan (RMP).

**Research questions**: There are two main research questions that will be evaluated:

**Research Question 1**
What are the utilization patterns of tofacitinib in the US with regard to on-label and off-label use?

**Research Question 2**
What are the incidence rates of safety events of interest in adult UC patients treated with tofacitinib (including both the immediate-release [5 mg and 10 mg twice daily] and the extended-release [11 mg and 22 mg once daily] formulations) in routine clinical care?

- **Objectives**: The study objectives are described below as follows:

  To address the first research question, the objective will be to describe the utilization patterns of tofacitinib in the US with regard to on-label and off-label use by:

  - Estimating the proportion of tofacitinib users who receive the drug for the approved indications during the study period
  - Describing the characteristics of patients who are prescribed tofacitinib for on-label, off-label and unknown indications in terms of the following:
    - Demographics (e.g., age, sex);
    - Comorbidities;
    - Prior and concurrent medications;
    - Prescribed daily dose and duration of tofacitinib therapy
  - Estimating the proportion of UC patients on 5 mg twice daily or 11 mg once daily and 10 mg twice daily or 22 mg once daily maintenance therapies
  - Estimating the proportion of non-UC patients on 10 mg twice daily or 22 mg once daily therapy
  - Estimating the proportion of patients with approved indications who have $\geqslant 1$ thrombosis risk factors and are prescribed tofacitinib, overall and stratified by dose
  - Estimating the proportion of TNFi-naïve UC patients prescribed tofacitinib pre and post 01 July 2019

To address the second research question, the objectives will be as follows:

1. To estimate the incidence rate of malignancy, excluding non-melanoma skin cancer (NMSC), among adult UC patients who initiate tofacitinib in the course of routine clinical care, and

2. To estimate the incidence rates of other safety events of interest, including (but not limited to) lung cancer, lymphoma, NMSC, opportunistic infections (e.g. tuberculosis), major adverse cardiac events (MACE), venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]), myocardial infarction (MI), hepatic events, serious infections, herpes zoster (HZ) reactivation, progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, interstitial lung disease (ILD), fractures, surgery for UC and death amongadult UC patients who initiate tofacitinib in the course of routine clinical care. For contexualization and risk characterization purposes, incidence rates of these safety events of interest in adult UC patients initiating treatment with other approved systemic agents, as well as adult UC patients naïve to both biologics and immunomodulators/immunosuppressants will also be assessed.

- **Study design**: This is a drug utilization and active surveillance study utilizing secondary data from the International Business Machines (IBM) Watson Health MarketScan® Research Databases, a US administrative healthcare claims database, from November 2012 (time of first of US approval for tofacitinib) through to 30 June 2025 (end of data collection).

- **Population**: The study population will include all patients enrolled in the Marketscan database during the study period who have received ≥1 prescription of tofacitinib. Additionally, for the active surveillance population (to be used for the estimation of incidence rates for the safety events of interest in adult UC patients as described above), a sub-population will be created which will include adult UC patients aged ≥18 years enrolled in the Marketscan database who are initiating treatment with tofacitinib in the course of routine clinical care (Cohort 1). For contextualization and risk characterization purposes, the study will also include the following treatment cohorts: UC patients who initiate biologics, overall and stratified by TNFi/non-TNFi use and number of previous biologic treatments (Cohort 2); UC patients who initiate immunomodulators/immunosuppressants without concurrent biologics (Cohort 3); UC patients naïve to both biologics and immunomodulators/immunosuppressants (Cohort 4).

- **Variables**: The study variables will include baseline patient characteristics (i.e., clinical and demographic characteristics, comorbidities, and current and past therapies). To allow for the evaluation of drug utilization patterns, indication for tofacitinib use (classified as on-label, off-label, or unknown) will be characterized, and prescribed daily dose and duration of tofacitinib therapy will also be captured. For the active surveillance portion of the study, the primary safety event of interest is malignancy, excluding non-melanoma skin cancer (NMSC); other key safety events of interest include (but are not limited to) the following: lung cancer, lymphoma, NMSC, serious and opportunistic infections, hepatic events, venous thromboembolism and cardiovascular events, MI, progressive multifocal leukoencephalopathy, gastrointestinal perforations, ILD, fractures, surgery for UC, and death (note that due to database limitations, only in-hospital mortality can be captured).

- **Data source**: The IBM Watson Health MarketScan® Research Databases, a large US administrative healthcare claims database, will be used as the data source for this analysis. The MarketScan claims databases contain 143 million unique patients since 1996. It is a nationally representative data sample of Americans with employer-provided health insurance, as well as Medicare, and contains complete information on outpatient prescriptions and both inpatient and outpatient diagnoses.

- **Study size**: This is a descriptive study and all eligible patients during the study period in the Marketscan claims database who have received ≥1 tofacitinib prescription will be included, with no upper limit on the sample size. There are 11,857 patients who have received at least one prescription of tofacitinib in 2016-2018 IBM Marketscan data. Based on the same data, , there are an estimated 59,080 patients with either one inpatient diagnosis of UC, or at least two outpatient diagnoses of UC, with at least one of these two outpatient codes documented by a gastrointestinal specialist.

- **Data analysis**: This analysis will include descriptive summaries of baseline variables, proportion of tofacitinib users who receive the drug for the approved indications during the study period, and descriptive analysis of patients who are prescribed tofacitinib for on-label, off-label and unknown indications (demographics, comorbidities, prior and current medications, and prescribed daily dose and duration of tofacitinib therapy). Among patients with on-label (approved) indications (i.e. RA, PsA, UC, pcJIA), tofacitinib dose will be assessed, and classified as on-label dose or off-label dose according to each prescription of tofacitinib. The proportion of tofacitinib prescriptions with off-label dosing, stratified by approved indication, will be estimated. To further assess on-label/off-label use of tofacitinib, the proportion of TNFi-naïve UC patients prescribed tofacitinib prior to 01 July 2019 (on-label) and post 01 July 2019 (off-label) will also be estimated and described. Additionally, to further understand off-label dosing among patients with non-UC approved indications such as RA, PsA and pcJIA, the proportions of non-UC patients on 10 mg twice daily/22 mg once daily therapy will also be estimated and reported.

  As well, among UC patients specifically, the proportion of UC patients on 5 mg twice daily/11 mg once daily and 10 mg twice daily/22 mg once daily maintenance therapies, as well as the proportion of patients with approved indications (i.e. RA, PsA, UC, pcJIA) with ≥1 thrombosis risk factors who are prescribed tofacitinib (overall and stratified by dose) will also be estimated.

  Additionally, incidence rates of the safety events of interest as described above in all study cohorts will be estimated.

- **Milestones**:

  Start of data collection: June 2020[1]
  End of data collection: June 2025
  Interim report 1: June 2022
  Interim report 2: June 2024
  Final study report: June 2026



[1] This represents start of data collection for the active surveillance portion of the study. Start of data collection for the drug utilization study will be March 2021.

## 5. AMENDMENTS AND UPDATES

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| 2 | January 2021 | Substantial | Pass information table | Updated to reflect changes in study title and objectives.<br><br>Addition of EU PAS registration number and updates to protocol date, version, and product reference number. | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 1 | Table of contents updated to include additional sections for drug utilization study component added to protocol, and additional section to define index date for drug utilization and active surveillance components | Amendment of protocol to include drug utilization study component |
| | | Administrative | Section 2 | List of abbreviations updated to include new abbreviations, and to update definition for VTE from venous thromboembolic events to venous thromboembolism | Editorial changes |
| | | Substantial | Section 4 | Significant and editorial changes to abstract to reflect addition of drug utilization component to study protocol, including updates to study title to reflect both drug utilization and active surveillance components, updates to rationale and background, research questions and objectives, study design, | Amendment of protocol to include drug utilization study component |

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| | | | | population, variables, study size, data analysis and milestones. | |
| | | Administrative | Section 6 | Update to study milestones to reflect start date of drug utilization component of study, and change to date of final report submission to within 12 months of the end of data collection | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 7 | Updates to rationale and background to provide more information on approved indications/dose in the US and changes to overall goal of study to include drug utilization component<br><br>Specification that study is not only a commitment to US FDA, but also a category 3 study in the European Union risk management plan | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 8 | Updated to include research questions and objectives for drug utilization component | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 9.1 | Updated study design information to include new study observation period (from November 2012 (time of first of US approval for tofacitinib) through to June 2025); updates to study description to include analysis to | Amendment of protocol to include drug utilization study component |

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| | | | | assess tofacitinib utilization patterns | |
| | | Substantial | Section 9.2.1 | Updated to specify inclusion criteria for drug utilization component<br><br>Clarifications and editorial changes to inclusion criteria for active surveillance component | Amendment of protocol to include drug utilization study component<br><br>Editorial changes |
| | | Substantial | Section 9.2.2 | Updated to specify that no exclusion criteria will be applied for the drug utilization component | Amendment of protocol to include drug utilization study component |
| | | Administrative | Section 9.3 | Editorial changes | Editorial changes |
| | | Substantial | Section 9.3.1 | Clarification to specify baseline variables for both drug utilization and active surveillance components<br><br>Addition of history of heart failure, prior TNFi use and use of oral contraceptives/hormonal therapy as baseline variables | Amendment of protocol to include drug utilization study component<br><br>Clarifications/editorial changes |
| | | Substantial | Section 9.3.1.1 | New sub-section to define thrombosis risk factors | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 9.3.2 | New sub-section to define on-label and off-label use for drug | Amendment of protocol to include drug utilization study component |

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| | | | | utilization component of study | |
| | | Substantial | Section 9.3.3 | New sub-section to define prescribed daily dose and duration of tofacitinib therapy for drug utilization component of study | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 9.3.4 | New section to define index dates for drug utilization component (Section 9.3.4.1) and active surveillance component (Section 9.3.4.2) | Amendment of protocol to include drug utilization study component<br><br>Clarification of index date |
| | | Substantial | Section 9.3.5 | Updated to include illustration for as-treated approach with the 90-day extension period, and to specify additional sensitivity analysis to be conducted for this approach<br><br>Editorial change to section title | Clarification of follow-up in active surveillance component<br><br>Editorial changes |
| | | Substantial | Section 9.3.6 | Updated to include endpoint of interest for drug utilization component of study<br><br>Editorial changes to safety outcomes of interest for active surveillance component | Amendment of protocol to include drug utilization study component<br><br>Editorial changes |
| | | Substantial | Section 9.5 | Updated study size to provide preliminary data on number of patients with $\geqslant 1$ tofacitinib prescription in data source | Amendment of protocol to include drug utilization study component |

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| | | Administrative | Section 9.7 | Editorial changes | Editorial changes |
| | | Substantial | Section 9.7.1 | New sub-section to provide overview of analysis plan for drug utilization component of study | Amendment of protocol to include drug utilization study component |
| | | Substantial | Section 9.7.2 | Updated to specify subgroup analyses for active surveillance component | Clarifications to specify subgroup analyses for active surveillance component |
| | | Substantial | Section 9.7.3 | Updated to note that interim data from drug utilization component of study will be included<br><br>Editorial changes | Amendment of protocol to include drug utilization study component<br><br>Editorial changes |
| | | Substantial | Section 9.7.4 | Updated to note that final data from drug utilization component of study will be included<br><br>Editorial changes | Amendment of protocol to include drug utilization study component<br><br>Editorial changes |
| | | Administrative | Section 9.9 | Editorial changes to reflect amendment of protocol to include drug utilization study component | Editorial changes to reflect amendment of protocol to include drug utilization study component |
| | | Administrative | Section 12 | Editorial changes | Editorial changes |
| | | Substantial | Section 14 | Updated to include new table | Editorial change |
| | | Administrative | Annex 2 | Signature date for Encepp checklist | Editorial change |

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| 3 | 30 September 2024 | Administrative | Title page | Editorial changes to section title | Editorial changes |
| | | Substantial | Title page | Updated to include additional safety events of interest<br><br>Updated to reflect stratification in subgroup analyses | Amendment of protocol to include additional safety events of interest<br><br>Amendment of protocol to reflect individual dosing analyses |
| | | Administrative | Section 2 | List of abbreviations updated to include new abbreviations for HMA and RWD | Editorial changes |
| | | Administrative | Section 3 | Editorial changes to responsible parties | Editorial changes |
| | | Administrative | Section 4 | Editorial changes to abstract | Editorial changes |
| | | Substantial | Section 4 | Updated to include additional safety events of interest | Amendment of protocol to include additional safety events of interest |
| | | Administrative | Section 6 | Editorial changes to milestones | Editorial changes |
| | | Substantial | Section 8 | Updated to include additional safety events of interest<br><br>Updated to reflect stratification in subgroup analyses | Amendment of protocol to include additional safety events of interest<br><br>Amendment of protocol to reflect individual dosing analyses |
| | | Administrative | Section 9.2.1. | Editorial changes | Editorial changes |

| Version Identifier | Date | Amendment Type (substantial or administrative) | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|---|
| | | Substantial | Section 9.3.6. | Updated to include additional safety events of interest | Amendment of protocol to include additional safety events of interest |
| | | Substantial | Section 9.7.2 | Updated to reflect stratification in subgroup analyses | Amendment of protocol to reflect individual dosing analyses |
| | | Substantial | Section 9.7.4 | Updated to reflect stratification in subgroup analyses | Amendment of protocol to reflect individual dosing analyses |

## 6. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | 30 June 2020* |
| End of data collection | 30 June 2025 |
| Interim report 1 | 30 June 2022 |
| Interim report 2 | 30 June 2024 |
| Registration in the HMA-EMA Catalogues of RWD Studies | Prior to start of data collection |
| Final study report | 30 June 2026 |

*This represents the start of data collection for the active surveillance portion of the study. Start of data collection for the drug utilization study will be 31 March 2021.

## 7. RATIONALE AND BACKGROUND

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) characterized by chronic inflammation of the gastrointestinal tract, marked by an abnormal immune response. UC is restricted to the colon and affects the mucosa of the gut[1]. As a result of the inflammatory reaction, the intestinal wall is damaged, frequently leading to bloody diarrhea and abdominal pain.

UC presents significant health and socioeconomic burdens for the individual patient and society[6,7,8]. There is currently no cure for UC[1]. Moderate-to-severe UC often requires treatment with systemic agents, such as glucocorticoids and azathioprine[9], many of which are associated with infectious, cardiovascular, gastrointestinal and malignant adverse events[10, 11]. Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the United States (US) in May 2018 at a dose of 5 mg twice daily or 10 mg twice daily for the treatment of adults with moderate-to-severe UC. In July 2019, the US prescribing information (USPI) was updated to note that tofacitinib should be prescribed for adult patients with moderate-to-severe UC who have had an inadequate response or who are intolerant to tumor necrosis factor inhibitors (TNFis). In December 2019, the extended-release formulation was also approved for UC patients at a dose of 11 mg once daily and 22 mg once daily. Use of tofacitinib in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Tofacitinib is also currently approved for three other indications in the US, and these include in adults with moderate-to-severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX), in adults with active psoriatic arthritis who have had an inadequate response or intolerance to MTX or other disease-modifying antirheumatic drugs (DMARDs), and in patients ≥2 years with active polyarticular course

juvenile idiopathic arthritis (pcJIA). For RA, PsA and pcJIA patients, use of tofacitinib in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. Additionally, for RA and PsA patients, only the 5 mg twice daily and 11 mg once daily dosing regimens are approved; the 10 mg twice daily and 22 mg once daily dosing regimens are not indicated for use in non-UC patients. For pcJIA patients, only the 5 mg twice daily dosing regimen is approved. Due to the potential for off-label use of the 10 mg twice daily and 22 mg once daily dosing regimens in non-UC patients, as well as the potential for use of tofacitinib in non-indicated populations, it would be useful to understand the patterns of post-approval use in the US.

In addition, understanding of long-term safety associated with real-world tofacitinib use, including the potential risk of malignancy and other safety events of interest, is needed. Follow up of large cohorts of patients over a long period can help in the evaluation of any potential risk of malignancy, as well as other potential safety events of interest that may be associated with tofacitinib treatment. It is important that surveillance also examines patient co-morbidities which may influence the occurrence of safety events, as well as mortality. Active surveillance studies help assess the risk of safety events of interest overall and within strata of disease severity, treatment history, patient co-morbidities or risk factors and other concomitant therapy.

To understand the patterns of tofacitinib use in the US, as well as to characterize the risk of safety events of interest that may be associated with its use, a non-interventional, drug utilization and active surveillance study will be conducted using data from the International Business Machines (IBM) Watson Health MarketScan® Research Databases.
This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the US Food and Drug Administration (FDA). It is also a category 3 study in the tofacitinib European Union (EU) risk management plan (RMP).

## 8. RESEARCH QUESTIONS AND OBJECTIVES

The research questions and associated objectives for this study are as follows:

**Research Question 1**:
What are the utilization patterns of tofacitinib in the US with regard to on-label and off-label use?

**Objectives:**

- Estimate the proportion of tofacitinib users who receive the drug for the approved indications during the study period
- Describe the characteristics of patients who are prescribed tofacitinib for on-label, off-label and unknown indications in terms of the following:
    - Demographics (e.g., age, sex);

- Comorbidities;
- Prior and concurrent medications;
- Prescribed daily dose and duration of tofacitinib therapy

- Estimate the proportion of UC patients on 5 mg twice daily or 11 mg once daily and 10 mg twice daily or 22 mg once daily maintenance therapies
- Estimate the proportion of non-UC patients on 10 mg twice daily or 22 mg once daily therapy
- Estimate the proportion of patients with approved indications who have ≥1 thrombosis risk factors and are prescribed tofacitinib, overall and stratified by dose
- Estimate the proportion of TNFi-naïve UC patients prescribed tofacitinib pre and post 01 July 2019

**Research Question 2**:

What are the incidence rates of safety events of interest in adult ulcerative colitis (UC) patients treated with tofacitinib (including the immediate-release formulation [dosed as 5 mg and 10 mg twice daily] and the extended-release formulation [dosed as 11 mg and 22 mg once daily] formulations) in the course of routine clinical care?

**Primary Objective**:
The primary objective is to estimate the incidence rate of malignancy, excluding non-melanoma skin cancer (NMSC), among adult UC patients who initiate tofacitinib in the course of routine clinical care.

**Secondary Objective:**
The secondary objective is to estimate the incidence rates of other safety events of interest among adult UC patients who initiate tofacitinib in the course of routine clinical care. These other safety events include (but may not be limited to) the following:

- Lung cancer
- Lymphoma
- NMSC
- Serious infections
- Opportunistic infections (e.g. tuberculosis)
- Herpes zoster (HZ) reactivation
- Major adverse cardiac events (MACE)
- Venous thromboembolism (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE])
- Myocardial Infarction (MI)
- Hepatic events

- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Interstitial lung disease (ILD)
- Fractures
- Surgery for UC
- Death

For contextualization and risk characterization purposes, the incidence rates of the same safety events (listed in the primary and secondary objectives above) in adult UC patients initiating treatment with other approved systemic agents, as well as those patients naïve to biologics and immunomodulators/immunosuppressants will also be assessed. Therefore in total, incidence rates will be estimated within the following groups:

1. Cohort 1 (Tofacitinib cohort): UC patients initiating tofacitinib, overall and independently stratified by dose (5 mg twice daily,11 mg once daily, 10 mg twice daily, 22 mg once daily) and prior biologic use (i.e. patients naïve to biologics vs. patients with prior biologic use)

Contextualization Cohorts:

2. Cohort 2 (Biologics cohort): UC patients who initiate biologics,with/without concurrent immunomodulators/immunosuppressants, overall and independently stratified by TNFi/non-TNFi use and number of previous biologic treatments
3. Cohort 3 (Immunomodulators/immunosuppressants cohort): UC patients who initiate immunomodulators/immunosuppressants (methotrexate [MTX], azathioprine [AZA], mercaptopurine [6-MP]) without concurrent biologics
4. Cohort 4 (Naïve cohort): UC patients naïve to both biologics and immunomodulators/immunosuppressants

Patients in the naïve cohort are expected to have milder disease relative to patients in the other 3 cohorts.

## 9. RESEARCH METHODS

### 9.1. Study Design

This is a descriptive, drug utilization and active surveillance, secondary data collection study of patients with ≥1 tofacitinib prescription in the IBM Watson Health MarketScan® Research Databases from November 2012 (time of first of US approval for tofacitinib) through to 30 June 2025.

To assess tofacitinib utilization patterns, the proportion of tofacitinib users who receive the drug for the approved indications during the study period will be estimated, and the demographic and clinical characteristics patients who are prescribed tofacitinib for on-label, off-label, and unknown indications will also be described. Among patients with on-label (approved) indications (i.e. RA, PsA, UC, pcJIA), the proportion of tofacitinib prescriptions

with off-label dosing, stratified by approved indication, will be estimated. Additionally, the proportions of UC patients on 5 mg twice daily/11 mg once daily and 10 mg twice daily/22 mg once daily maintenance therapies, non-UC patients on 10 mg twice daily/22 mg once daily therapy and patients with approved indications who have ≥1 thrombosis risk factors and are prescribed tofacitinib (overall and stratified by dose), as well as the proportion of TNFi-naïve UC patients prescribed tofacitinib pre and post 01 July 2019 will be described. To characterize the risk of the various safety events of interest, incidence rates and associated 95% confidence intervals (CIs) will be calculated in the four cohorts described in Section 8. No a priori hypotheses are specified.

### 9.2. Setting

The IBM Watson Health MarketScan® Research Databases is a US administrative healthcare database containing 143 million unique patients since 1996. It is a nationally representative data sample of Americans with employer-provided health insurance, as well as Medicare, and contains complete information on outpatient prescriptions and both inpatient and outpatient diagnoses.

#### 9.2.1. Inclusion Criteria

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

##### 9.2.1.1. Drug Utilization Study

To assess utilization patterns of tofacitinib use, all patients enrolled in the Marketscan database during the study observation period (i.e. from time of first US approval for tofacitinib in 2012 through to end of data collection in 2025) who have received ≥1 prescription of tofacitinib will be included.

##### 9.2.1.2. Active surveillance study

The active surveillance population to be used for the estimation of the incidence rates of the safety events of interest will be a subset of the population described above, and will include all adult UC patients aged ≥18 years who are enrolled in the Marketscan database from the time of approval of tofacitinib for UC in the US (May 2018) through to the end of data collection (June 2025) for the study. UC patients will be identified via ICD-10 codes listed in Table 1. Using all available data, UC patients must have at least one UC diagnosis code from an inpatient visit, or at least two occurrences of a UC diagnosis code from outpatient vists, with at least one of the two outpatient codes documented by a gastrointestinal specialist. UC codes assigned on different dates do not need to be the same to qualify. At least 12 months of continuous (i.e., no more than a 30-day gap) database enrollment before index date is required to enable analysis of baseline patient and disease characteristics that may be important modifiers of the relationship of UC with safety endpoints of interest. Index date is defined in the treatment cohort inclusion criteria listed in the subsections below.

**Table 1. ICD Codes for UC Diagnoses within MarketScan Database**

| ICD-9 Code | Diagnosis | ICD-10 code | Diagnosis |
|---|---|---|---|
| 556 (no 3rd digit) | Ulcerative colitis | | |
| 556.0 | Ulcerative enterocolitis | K51.8 (all billable codes under K51.8) | Other UC |
| 556.1 | Ulcerative ileocolitis | K51.8 (all billable codes under K51.8) | Other UC |
| 556.2 | Ulcerative proctitis | K51.2 (all billable codes under K51.2) | Ulcerative (Chronic) Proctitis |
| 556.3 | Ulcerative proctosigmoiditis | K51.3 (all billable codes under K51.3) | Ulcerative (Chronic) Rectosigmoiditis |
| 556.5 | Left-sided ulcerative colitis | K51.5 (all billable codes under K51.5) | Left Sided Colitis |
| 556.6 | Universal ulcerative colitis | K51.0 (all billable codes under K51.0) | Ulcerative (Chronic) Pancolitis |
| 556.8 | Other ulcerative colitis | K51.8 (all billable codes under K51.8) | Other Ulcerative Colitis |
| 556.9 | Ulcerative colitis, unspecified | K51.9 (all billable codes under K51.9) | Ulcerative Colitis, Unspecified |

Patients may switch between the tofacitinib and contextualization cohorts over time if inclusion/exclusion criteria listed below are met. Additionally, patients will be eligible for entry into a particular cohort each time they start a new therapy within the same drug class. For acute endpoints, patients will be censored from a particular cohort when they start a new therapy in a different drug class. For the endpoint of MACE, for example, patients in Cohort 1 (UC patients initiating treatment with tofacitinib) will be censored if and when they switch to a specific biologic agent, but will be eligible for subsequent inclusion into Cohort 2 (patients initiating treatment with biologics). For non-acute outcomes such as malignancy and death, outcomes will be evaluated using a "once exposed always at risk" paradigm (as described in Section9.3.5).

Formal definitions of index dates/start of follow-up are provided in Sections 9.3.4.2 and 9.3.5.Details of exposure measurement (e.g., allowing specified gaps between prescriptions in continuous exposure, etc.) will be detailed in the statistical analysis plan (SAP).

#### 9.2.1.2.1. Cohort 1 (Tofacitinib cohort): Adult UC Patients Treated with Tofacitinib

1. Initiation of tofacitinib as captured in Marketscan since 30 May 2018 (i.e. first tofacitinib prescription occurring either after the first UC diagnosis code from an inpatient visit or after the second UC diagnosis code from an outpatient visit and following US approval of tofacitinib for UC).

   Note that in the US, as per the US prescribing information (USPI), tofacitinib is not expected to be prescribed to newly diagnosed UC patients, and since UC is a chronic condition, it is expected that the majority of UC patients receiving tofacitinib would have previously been prescribed other forms of UC therapy. For those patients with

an outpatient diagnosis of UC, it is unlikely that many, if any at all, will receive a prescription for tofacitinib after the first UC diagnosis code (and before the second UC diagnosis code).

2. Patients with either 1 UC diagnosis code from an inpatient visit or ⩾2 of any of the ICD-10 codes for UC in Table 1 from an outpatient visit prior to the index date (i.e. date of first prescription of tofacitinib) (at least one of the two required UC diagnoses from outpatient visits must be made by a gastrointestinal specialist.

   As per recommendations from the USPI, patients in this cohort may not be on potent immunomodulators/immunosuppressants concurrently.

#### 9.2.1.2.2. Cohort 2 (Biologics cohort): Adult UC Patients Treated with Biologics

1. Initiation of biologic therapy (i.e. first prescription for a specific TNFi or non-TNFi agent) as captured in Marketscan since 30 May 2018

2. Patients with either 1 UC diagnosis code from an inpatient visit or ≥2 of any of the ICD-10 codes for UC in Table 1 from an outpatient visit prior to index date (i.e. date of first prescription for a specific biologic agent; at least one of the two required diagnoses from outpatient visits must be made by a gastrointestinal specialist)

   Patients in this cohort will be assessed overall, and independently stratified by TNFi and non-TNFi use. Patients may also be on immunomodulators/immunosuppressants concurrently.

#### 9.2.1.2.3. Cohort 3 (Immunomodulators/immunosuppressants cohort): Adult UC Patients Treated with Immunomodulators/Immunosuppressants without concurrent Biologics

1. Initiation of immunomodulator/immunosuppressant therapy (i.e. first prescription for a specific immunomodulator/immunosuppressant agent) as captured in Marketscan since 30 May 2018 (without concurrent biologics)

2. Patients with either 1 UC diagnosis code from an inpatient visit or ≥2 of any of the ICD-10 codes for UC in Table 1 from an outpatient visit prior to index date (i.e. date of first prescription for an immunomodulator/immunosuppressant agent; at least one of the two required diagnoses from outpatient visits must be made by a gastrointestinal specialist)

#### 9.2.1.2.4. Cohort 4 (Naive cohort): Biologic/immunomodulator/immunosuppressant-naïve Cohort

1. Naive to biologics/immunomodulators/immunosuppressants using all available data

2. Patients with either 1 UC diagnosis code from an inpatient visit or ≥2 of any of the ICD-10 codes for UC in Table 1 before start of follow-up (at least one of the two required diagnoses from outpatient visits must be made by a gastrointestinal

specialist). For these patients, start of follow-up will be defined by an index date as described in Section 9.3.4.2.

### 9.2.2. Exclusion Criteria

To assess tofacitinib utilization patterns, no exclusion criteria will be applied. However, for the active surveillance population which will consist of a subset of the study population, patients not meeting the inclusion criteria for any of the respective cohorts described above will be excluded.

## 9.3. Variables

A summary of all relevant study variables is provided in the sections below. Detailed definitions, including relevant ICD codes and procedure codes used to define safety events of interest for the active surveillance portion of the study and other variables, will be included in the SAP.

### 9.3.1. Baseline Data

Baseline data for both the drug utilization and active surveillance components of the study will include the following, as appropriate:

- Age (years) at index date
- Sex (male/female)
- Age of UC onset (years)/years since UC diagnosis (i.e. from date of first inpatient UC diagnosis code or second outpatient UC diagnosis code to index date)
- Smoking status (yes/no as per algorithm based on diagnosis and procedure codes[24])
- Comorbidities (within 12 months of index date for non-malignancy events, and ever for malignancy events) e.g.
    - history of malignancies,
    - history of serious infection,
    - history of opportunistic infection,
    - history of herpes zoster,
    - history of venous thromboembolism,
    - history diabetes mellitus,
    - history of myocardial infarction [MI],
    - history of heart failure

  - history of hypertension,
  - history of inherited coagulation disorders

- Prior TNFi use (using all available data)
- Concomitant use of immunomodulators/immunosuppressants at index date
- Use of the following medications within 12 months of index date:
  - oral contraceptives or hormonal therapy
  - oral steroids,
  - oral nonsteroidal anti-inflammatory drugs [NSAIDs],
  - antimicrobials,
  - anticoagulants,
  - beta blockers,
  - bisphosphonates,
  - narcotics,
  - proton pump inhibitors [PPIs]
  - statins

#### 9.3.1.1. Thrombosis Risk Factors

To assess risk factors for MACE and to allow for the estimation of the proportion of patients with approved indications (i.e. RA, PsA, UC, pcJIA) who have with ≥1 thrombosis risk factors and are prescribed tofacitinib, the following thrombosis risk factors will be evaluated at baseline and/or, for some risk factors, within specific time periods prior to index date as specified below:

- Age
- Smoking status
- Use of combined hormonal contraceptives or hormone replacement therapy within 3 months of index date
- Previous VTE
- History of MI within previous 3 months prior to index date

- History of heart failure
- History of hypertension
- History of malignancy (using all available data)
- Diabetes
- Inherited coagulation disorders

### 9.3.2. Definition of On-Label and Off-Label Use for Assessing Utilization Patterns

The following table summarizes the date tofacitinib was approved in the US and the approved dose for each of the three approved indications.

**Table 2. Summary of approved indications and dosages for tofacitinib in the US**

| Indication | Date approved in the US | Approved dose | Limitations for use |
|---|---|---|---|
| RA | 06 Nov 2012 | 5 mg immediate-release tablets twice daily | Not recommended for use in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine |
| | 24 Feb 2016 | 11 mg prolonged release tablets once daily | |
| PsA | 14 Dec 2017 | 5 mg immediate-release tablets twice daily | Not recommended for use in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine |
| | 14 Dec 2017 | 11 mg prolonged release tablets once daily | |
| UC | 30 May 2018 | 5 mg or 10 mg immediate-release tablets twice daily | Not recommended for use in combination with biological therapies for UC or potent immunosuppressants such as azathioprine and cyclosporine |
| | 12 December 2019 | 11 mg or 22 mg prolonged release tablets once daily | |
| pcJIA | 25 September 2020 | 5 mg immediate-release tablets twice daily or weight-based equivalent twice daily (tablet or oral solution) | Not recommended for use in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine |

pcJIA = polyarticular course juvenile idiopathic arthritis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis; US = United States

To evaluate indication for use, all patients' tofacitinib use will be classified as on-label indication, off-label indication or unknown indication associated with the first tofacitinib prescription during the observation period. Thus, for the purpose of

this analysis, on-label indication for use of tofacitinib will be defined, based on the date of the first prescription, as a prescription of the drug to:

1. An adult (patients aged ≥18 years), AND

2. After November 2012, a patient whose first tofacitinib prescription occurred after a diagnosis of RA (defined as either as having ≥ 1 inpatient or ≥ 2 outpatient RA diagnosis codes on two unique calendar days, with at least one from a rheumatologist), OR

3. After December 2017, a patient whose first tofacitinib prescription occurred after a diagnosis of PsA (defined as either as having ≥ 1 inpatient or ≥ 2 outpatient PsA diagnosis codes on two unique calendar days, with at least one from a rheumatologist), OR

4. Between May 2018 and July 2019, a patient whose first tofacitinib prescription occurred after a diagnosis of UC (defined as the first UC diagnosis code from an inpatient visit or after the second UC diagnosis code from an outpatient visit), OR

5. After July 2019, a patient whose first tofacitinib prescription occurred after a diagnosis of UC (as defined above) AND after evidence of prior TNFi use (i.e. using all available data, a prescription for ≥1 TNFi agent prior to first tofacitinib prescription), OR

6. After September 2020, a patient aged ≥2 years whose first tofacitinib prescription occurred after a diagnosis of pcJIA (defined as either as having ≥ 1 inpatient or ≥ 2 outpatient pcJIA diagnosis codes on two unique calendar days, with at least one from a rheumatologist)

In contrast, off-label indications will be defined as use of tofacitinib among patients with other diagnoses (i.e. lack of diagnosis codes for RA, PsA, UC or JIA) not fulfilling any of the conditions outlined above. If off-label use among non-approved indications occurs, it is expected that tofacitinib will be more likely used among patients with other non-approved rheumatic conditions (e.g. psoriasis, ankylosing spondylitis) or other non-approved IBD conditions (e.g. Crohn's disease). Thus off-label indications will be identified by broadly targeting diagnosis codes for other non-approved rheumatic and IBD conditions. Additionally, if the indications for which tofacitinib is prescribed cannot be determined from the available data, these will be classified as unknown indications and will evaluated separately as described in Section 9.7.1.

Among patients with on-label indications, tofacitinib dose will be assessed. For each of these patients, every tofacitinib prescription will be classified as on-label or off-label based on the labeled dose for the patient's indication at the time of prescription. Thus, for the

purposes of this analysis, on-label dose of tofacitinib will be defined, based on each tofacitinib prescription, using the following criteria:

1. Between November 2012 and November 2017, a prescription of tofacitinib 5 mg twice daily occurring only after a diagnosis of RA (as defined above)
2. Between February 2016 and November 2017, a prescription of tofacitinib 11 mg once daily occurring only after a diagnosis of RA (as defined above)
3. After December 2017, a prescription of tofacitinib 5 mg twice daily or 11 mg once daily occurring only after a diagnosis of either RA or PsA (as defined above)
4. After May 2018, a prescription of tofacitinib 5 mg twice daily occurring only after a diagnosis of either RA, PsA or UC (as defined above)
5. After May 2018, a prescription of tofacitinib 10 mg twice daily occurring only after a diagnosis of UC (as defined above)
6. After December 2019, a prescription of tofacitinib 11 mg once daily or 22 mg once daily occurring only after a diagnosis of UC (as defined above)
7. After September 2020, a prescription of tofacitinib 5 mg twice daily occurring only after a diagnosis of RA, PsA, UC or pcJIA.

For each approved indication of tofacitinib (i.e. RA, PsA, UC, pcJIA), the proportion of tofacitinib prescriptions with off-label dosing will be estimated as described in Section 9.7.1.

### 9.3.3. Prescribed daily dose and duration of tofacitinib therapy

To assess utilization patterns, prescribed daily dose (DD) and duration of tofacitinib therapy will be described using days of supply and amount dispensed for patients who are prescribed tofacitinib for on-label, off-label and unknown indications.

Duration of tofacitinib therapy will be defined as the time from the date of the first ever tofacitinib prescription to the date of discontinuation of tofacitinib. The operational definitions for duration of tofacitinib therapy will be further elaborated in the SAP.

Prescribed DD will be calculated in milligrams per day, starting from the index date and using reported days' supply and dispensed amount, and will be stratified by indication for tofacitinib use, classified as on-label, off-label, or unknown. Further details will be provided in the SAP. DD will be time-varying and reported as a continuous and categorical variable:

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

To assess patients' tofacitinib dose while on maintenance therapy, tofacitinib maintenance dose will be defined as patients' tofacitinib dose post 16 weeks of the patient's first ever tofacitinib prescription (i.e. patient's recorded tofacitinib dose at ≥Week 17 after patient's first ever tofacitinib prescription).

### 9.3.4. Index Date

#### 9.3.4.1. Drug Utilization Study

For the drug utilization portion of the study, the date of the first prescription of tofacitinib during the study period is the index date.

#### 9.3.4.2. Active Surveillance Study

For the active surveillance portion of the study, index date will be defined as follows:

Cohort 1: This will be the date of first prescription for tofacitinib since 30 May 2018, following a diagnosis of UC as described in Section 9.2.1.2.1.

Cohort 2: This will be the date of first prescription for a specific biologic agent since 30 May 2018, following diagnosis of UC as described in Section 9.2.1.2.2. For patients with more than one biologic initiation, more than one index date will be defined (e.g., one for each biologic initiation).

Cohort 3: This will be the date of first prescription for a specific immunomodulator/immunosuppressant agent since 30 May 2018, following diagnosis of UC as described in Section 9.2.1.2.3. For patients with more than one immunomodulator/immunosuppressant initiation, more than one index date will be defined.

Cohort 4: This will be the date of UC diagnosis as described in Section 9.2.1.2.4, since 30 May 2018.

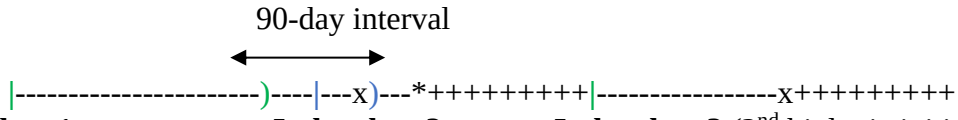
### 9.3.5. Follow-up in the active surveillance population

Patients in the active surveillance population will be followed from index date until first occurrence of each outcome of interest, treatment switch or discontinuation, with the appropriate outcome-specific extension to exposure (i.e. 90 day window for acute events, and "once-exposed always at risk" approach for non-acute events like malignancy as described below), and with death, lost medical/pharmacy coverage, and end of data collection (30 June 2025) treated as censoring events.

Acute events of interest in this study 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 reactivation, MACE, VTE, GI perforation, PML). 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. 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




**Index date 1** (1st biologic initiation) **Index date 2** (tofacitinib initiation) **Index date 3** (2nd biologic initiation)

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

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

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

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

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

A sensitivity analysis whereby 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 will also be conducted and further discussed in the SAP. 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 each patient, follow-up time contributing to one of the three treated cohorts will be calculated as the sum of dispensed medication days (based on days supply) plus the 90-day extension period.

For NMSC and malignancies, surgery for UC, and death (and as a sensitivity analysis for PML), the occurrences of which are expected to be delayed relative to the time of exposure, the outcomes will be evaluated from drug initiation until the first event or loss to follow up, 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.

Additionally, for patients experiencing a specific event of interest (except death), follow-up will be censored for that particular event; however follow-up will continue for all other events of interest.



### 9.3.6. Endpoints of Interest

To assess tofacitinib utilization patterns, the main endpoint of interest to be captured in the interim and final study reports will be the indication for tofacitinib use, classified as on-label, off-label, or unknown, based on medical events (diagnoses and/or medication use) identifiable around the time of the first ever tofacitinib prescription. The date of first prescription of tofacitinib during the study period is the index date as described in Section 9.3.4.1. All patients' tofacitinib use will be classified as on-label indication, off-label indication or unknown indication according to the first prescription of tofacitinib received, regardless of later prescriptions. The on-label, off-label and unknown indication classifications will be made based on the authorized indication(s) as of the index date.

For the active surveillance portion of the study, the safety events of interest (to be defined via ICD-code based algorithms in the SAP) which will also be captured in the interim and final study reports include the following:

- Malignancy, excluding NMSC
- Lung cancer
- Lymphoma
- NMSC
  - Serious infections
  - Opportunistic infections (e.g. tuberculosis)
  - HZ reactivation

- MACE
- VTE (DVT and PE)
- Myocardial Infarction (MI)
- Hepatic events
- PML (PML)
- GI perforations
- ILD
- Fractures
- Surgery for UC (e.g. colectomies, partial colectomies, and proctocolectomies; full list of procedures to be detailed in SAP)

- Death

Of note, due to limitations related to the Marketscan database, only in-hospital deaths can be captured (outcome will be defined via an algorithm currently under development, details of which will be outlined in the SAP). Deaths occurring in other environments such as home, non-hospital institutions, etc., cannot be captured.

The above list of safety endpoints may be extended with additional sub-diagnoses or new health-related outcomes as agreed to by study researchers and Sponsor before the interim reports and final study report. These decisions will be made prior to initiation of analyses and documented in the SAP kept on file by the Sponsor.

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

## 9.4. Data Source

### 9.4.1. IBM Watson Health MarketScan® Research Databases

The data source for this analysis will be the IBM Watson Health MarketScan® claims database, a US administrative healthcare claims database. This database contains 143 million unique patients since 1996. Its sample size is large enough to allow for a nationally representative data sample of Americans with employer-provided health insurance, as well as Medicare and contains information on outpatient prescriptions and both inpatient and outpatient diagnoses. IBM Watson Health MarketScan® Research Databases include Commercial Claims and Encounters (Commercial) Database, Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) Database, and the Lab Database. These databases represent healthcare claims information for individuals enrolled in various employer-sponsored healthcare plans. A subset of these individuals also receives benefits via Medicare supplemental insurance. The Commercial Database represents individuals covered under various commercial plans such as fee-for-service, capitated payment, preferred provider organizations, point-of-service, indemnity, and health maintenance organizations.

## 9.5. Study Size

This is a descriptive study and all eligible patients in Marketscan who have received ≥1 tofacitinib prescription from November 2012 (time of first US approval for tofacitinib) through to the end of data collection (30 June 2025) will be included, with no upper limit on the sample size. A preliminary analysis of the Marketscan database (using data from 2016

through to 2018) indicates that there are 11,857 patients who have received at least one prescription of tofacitinib, and59,080 patients who have at least 1 UC diagnosis from an inpatient visit or at least 2 UC diagnoses from outpatients visits, with at least one of these codes documented by a gastrointestinal specialist.

### 9.6. Data Management

Statistical analyses will be performed using SAS version 9.4 (Cary, NC). All analyses will be carried out under the direction of researchers at the University of Alabama, Birmingham (UAB) who will oversee all data analyses and provide direct biostatistical input. Statistical analysis will be completed only after all data have been entered, imported into and cleaned in SAS. To ensure the integrity and quality of the study results, UAB will follow standard operating procedures for programming validation for all analyses.

### 9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the Sponsor. However, a brief overview of the analysis plan is provided in the sub-sections below. The SAP may modify the plans outlined in the protocol; any major modifications of endpoint definitions or their analyses would be reflected in a protocol amendment.

#### 9.7.1. Assessment of tofacitinib utilization patterns

Categorical variables will be summarized using frequencies and proportions; continuous variables will summarized using means with standard deviations and/or medians with interquartile ranges, as appropriate. Age will be reported as a continuous variable and in clinically relevant categories, to identify off-label pediatric use (e.g. use in patients younger than 18 years prior to September 2020 and who do not have a pcJIA diagnosis) and use among elderly patients (i.e. 65 years or older).

The proportions of patients with an on-label, off-label, or unknown tofacitinib indication will be estimated with corresponding 95% confidence intervals (CIs). Patients who are prescribed tofacitinib for on-label, off-label and unknown indications will be described in terms of demographics (age, sex), comorbidities, prior and current medications (in terms of comedications not recommended for use while on tofacitinib i.e. biologic DMARDs, biologic therapies for UC or potent immunosuppressants such as azathioprine and cyclosporine as described in Table 2), as well as prescribed DD and duration of tofacitinib therapy. As it is expected that tofacitinib is more likely to be used off-label in non-approved rheumatic (e.g. psoriasis, ankylosing spondylitis) and IBD conditions (e.g. Crohn’s disease), to identify off-label indications, diagnosis codes for other non-approved rheumatic and IBD conditions will be targeted. Among patients with on-label (approved) indications (i.e. RA, PsA, UC, pcJIA), tofacitinib dose will be assessed (as described in Section 9.3.2) and classified as on-label dose or off-label dose according to each prescription of tofacitinib. The proportion of tofacitinib prescriptions with off-label dosing, stratified by approved indication, will be estimated.

To further assess on-label/off-label use of tofacitinib, the proportion of TNFi-naïve UC patients prescribed tofacitinib prior to 01 July 2019 (on-label) and post 01 July 2019 (off-label) will also be estimated and described. Additionally, to further understand off-label dosing among patients with non-UC approved indications such as RA, PsA and pcJIA, the proportions of non-UC patients on 10 mg twice daily/22 mg once daily therapy will also be estimated and reported.

Among UC patients, the proportion of UC patients on 5 mg twice daily/11 mg once daily and 10 mg twice daily/22 mg once daily maintenance therapies, as well as the proportion of patients with approved indications (i.e. RA, PsA, UC, pcJIA) who have ≥1 thrombosis risk factors and are prescribed tofacitinib, overall and stratified by dose, will also be estimated and described.

Patients will be followed from the date of first tofacitinib prescription until death or end of data collection (whichever comes first) to estimate prescribed DD, and cumulative duration of use during the study period.

### 9.7.2. Analysis of safety endpoints of interest

For the safety endpoints of interest, descriptive statistics, counts and proportions, cumulative incidence proportions, and crude incidence rates (i.e., number of events per person-years) and associated two-sided 95% confidence intervals will be calculated as appropriate. UC patients with a baseline history of an outcome of interest will be excluded from the calculation of the incidence rate for that particular outcome of interest (e.g. patients with a baseline history of malignancy will be excluded from the calculation of the incidence rate for malignancy).

Several subgroup analyses will be performed. These include (but are not limited to) stratification by:

- Tofacitinib dose (5 mg twice daily vs. 11 mg once daily vs. 10 mg twice daily vs. 22 mg once daily)
- Patient characteristics such as age at index date, including a subgroup analysis of patients <50 years vs. ≥50 years, and patients <65 years vs. ≥65 years
- For the outcomes of VTE and MACE, subgroup analysis of patients with ≥1 thrombosis risk factors (as defined in Section 9.3.1.1) vs. no thrombosis risk factors, and
- Key indicators of disease severity such as number of previous biologic treatments (i.e. prior biologic use vs. none; among those with prior biologic use, 1st biologic vs. 2nd biologic vs. ≥3 biologics)

This will be a time to first event analysis based on an index date defined for each cohort with appropriate censoring rules applied (based on therapy switches, end of study, etc.) for those

who do not experience an event by end of follow-up period. Rates will be expressed as the number of events/100 person-years of follow-up.

### 9.7.3. Interim Reports

Interim reports assessing tofacitinib utilizations patterns to-date and summarizing the crude incidence rates (with corresponding 95% confidence intervals) of safety events of interest will be provided as per the timeline in Section 6 (Milestones). These will include data on UC patients treated with tofacitinib and other approved systemic medications, and rates "on drug" and "ever since treatment start" accumulated in Marketscan to date. Only overall (non-stratified) results will be provided.

### 9.7.4. Final Study Report

In the final study report, data on the utilization patterns of tofacitinib will be provided as described in Section 9.7.1. For the analysis of safety events of interest, there will be some but limited flexibility to add additional safety endpoints and stratification, and it will contain populated tables in line with shells to be provided in the SAP.

In the final report, for the active surveillance portion of the study, the tofacitinib cohort will be analyzed overall and stratified by patient age, dose (5 mg twice daily vs. 11 mg once daily vs. 10 mg twice daily vs. 22 mg once daily), previous biologics use, VTE risk factors such as history of hypertension, and potentially other agreed upon strata determined prior to analysis and included in SAP filed with Sponsor. The general analytic approach will be descriptive and include incidence rates of safety events of interest within the tofacitinib cohort and within the contextualization cohort of those initiating treatment with a biologic, stratified by class of biologic (TNFi vs. non-TNFi), number of previous biologic treatments, monotherapy and combination therapy. For additional contextualization purposes, incidence rates will also be estimated for the other treatment cohorts.

## 9.8. Quality Control

A series of automated and semi-automated procedures will be used to assess the validity and consistency of the study dataset.

For raw data, the number of unique patients and unique records for each year will be evaluated. The number of unique patients, and unique records, will be compared year-by-year and file-by-file, to ensure relative stability of counts over time. Each variable in the dataset will be examined for completeness vs. missingness, allowable values (verified against the data dictionary, as appropriate), and range checks. These checks will enable identification of both *errors* (systematic transformation issues) and *anomalies* (unexpected data behavior).

Following analyses, all output will be verified against source document(s). Source data may be in final (or draft) production reports generated by analytic procedures (e.g. SAS).

### 9.8.1. Methods to correct inconsistencies or errors

Summary statistics will be tabulated for all variables and outliers identified. Outliers will be reconciled with additional electronic data sources, when available.

### 9.8.2. Methods to address missing data

Imputation for missing data points will not be performed in this descriptive study.

## 9.9. Limitations of the research methods

This study is designed to assess tofacitinib utilization patterns, as well as monitor its safety among US adult UC patients within the clinical practice setting using an administrative healthcare claims database. Strengths of the study include a large, demographically diverse cohort of UC patients allowing for the generation of robust incidence estimates for the various outcomes of interest.

Misclassification of exposure and endpoints and inability to obtain detailed clinical information are possible limitations due to the nature of claims databases. In addition, because the claims are collected for the purpose of payment and not research, in the case of drug administrations identified in the pharmacy record, presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over-the-counter or provided as samples by the physician will not be captured in the claims data. The presence of a diagnosis code on a medical claim may not represent true presence of a disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease.

To assess baseline patient smoking status, diagnosis and procedure codes will be used. Data from published literature[24] indicates that while this claims-based algorithm for smoking can identify smokers with very high specificity, its sensitivity is limited, thus suggesting that a large number of true/actual smokers may not be adequately captured in this study.

In addition, due to limitations related to the database, all-cause mortality cannot be assessed since only in-hospital deaths are captured. This may result in an underestimation of the outcome as deaths occurring in other environments (e.g. home, institutions, etc.,) cannot be captured. Additionally, due to privacy concerns, in-hospital deaths cannot be directly captured in the database, and must be estimated via use of an algorithm which will developed as part of this study and will not be able to be validated for use in claims databases. As such, in-hospital deaths may not be accurately captured in this study. For acute events, a 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. However, there is the possibility of potential misclassification of the exposure window for any treatments for which the half-life is shorter, leading to a potential underestimation of incidence rates for some outcomes.

As tofacitinib is a new UC medication, it is possible that patients treated with it will represent those with the most severe cases of disease, longer disease duration, history of multiple failed

UC therapies and physical comorbidities that place patients at risk for events. Channeling may present as increased rates of safety events of interest in the early phases of the study. Incidence rates from the contexualization 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. However, certain patient characteristics which may influence VTE risk (e.g. obesity and immobilization), cannot be reliably captured, and thus may limit data interpretation. Trend analyses may be conducted to evaluate rates in tofacitinib patients over time. Analysis may be unable to identify or control for any changes in rates due to changes in the treatment landscape.

Conclusions from this study may be limited to the duration of treatment captured. Finally, while these data may be generalizable to the commercially insured population and patients on Medicare, they may not be representative of those whose primary insurance is through Medicaid.

### 9.10. Other Aspects

Not applicable.

## 10. PROTECTION OF HUMAN SUBJECTS

### 10.1. Patient Information

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

### 10.2. Patient Consent

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

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

IRB approval will be sought for this protocol by the investigators. 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 study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology, and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Two interim summary reports and a final study report will be generated and submitted to regulatory authorities where applicable. Data may also be used in regulatory communications external to the US for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for publication.

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

## 13. REFERENCES

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. 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.

4. The Committee for Medicinal Products for Human Use. Draft guideline on the development of new medicinal products for the treatment of ulcerative colitis. CHMP/EWP/18463/2006 Revision 1. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500211431&mid=WC0b01ac058009a3dc. 21 July 2016.

5. 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

6. 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.

7. 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.

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

9. 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.

10. 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.

11. 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.

12. Ludvigsson, J. F., Otterblad Olausson, P., Pettersson, B. U., & Ekbom, A. (2009). The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European Journal of Epidemiology, 24(11), 659–667.

13. Wettermark, B., Hammar, N., Fored, C. M., et al. (2007). The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and Drug Safety, 16(7), 726–735.

14. Brooke, H. L., Talbäck, M., Hörnblad, J., et al. (2017). The Swedish cause of death register. European Journal of Epidemiology, 32(9), 765–773.

15. Barlow, L., Westergren, K., Holmberg, L., & Talbäck, M. (2009). The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncologica (Stockholm, Sweden), 48(1), 27–33.

16. Ludvigsson, J. F., Andersson, E., Ekbom, A., et al. (2011). External review and validation of the Swedish national inpatient register. BMC Public Health, 11(1), 450.

17. Ludvigsson, J. F., Svedberg, P., Olen, O., et al. (2019). The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. European Journal of Epidemiology, 1–15. http://doi.org/10.1007/s10654-019-00511-8

18. Ludvigsson, J. F., Almqvist, C., Bonamy, A.-K. E., et al. (2016). Registers of the Swedish total population and their use in medical research. European Journal of

Epidemiology, 1–12. http://doi.org/10.1007/s10654-016-0117-yhttp://doi.org/10.1007/s10654-016-0117-y

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

20. Centre for Epidemiology. The Swedish Medical Birth Register - A Summary of Content and Quality. In: National Board of Health and Welfare, ed., 2003. http://www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret/inenglish (accessed 15 May 2018).

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. Desai, RJ, Solomon, DH, Shadick, N, et al. Identification of smoking using Medicare data- A validation study of claims-based algorithms. Pharmacoepidemiol Drug Saf. 2016 Apr; 25(4): 472–475

## 14. LIST OF TABLES



## 15. LIST OF FIGURES

None.

## ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

**Study title:** An Active Surveillance, Post-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 a US Administrative Healthcare Claims Database

**EU PAS Register® number:** Pending (prior to the start of data collection)
**Study reference number (if applicable):** A3921347

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

Comments:

Protocol will be registered in the EU PAS register prior to the start of data collection.

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

[3] Date from which the analytical dataset is completely available.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☐ | ☐ | ☐ | |
| 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 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☒ | ☐ | ☐ | 9.1 |

Comments:

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| **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:

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| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period | ☒ | ☐ | ☐ | 6, 9.2.1 |
| 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.2, 9.4 |
| 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 8, 9.2 |
| 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.2 |

| Section 4: Source and study populations | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 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:

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| 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 |
| 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) | ☐ | ☐ | ☒ | |
| 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:

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|---|
| Details related to dosing to be provided in a statistical analysis plan (SAP) |

| 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? | ☐ | ☒ | ☐ | |
| 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) | ☐ | ☐ | ☒ | |
| 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:

| |
|---|
| Details related to outcome definition to be provided in a statistical analysis plan (SAP) |

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

Comments:

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| **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) | ☐ | ☐ | ☒ | |

Comments:

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| **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) | ☐ | ☒ | ☐ | |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☐ | ☒ | ☐ | |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☒ | ☐ | |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☒ | ☐ | |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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) | ☐ | ☐ | ☒ | |

Comments:

Details of covariate, exposure and outcome definitions 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? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☒ | ☐ | |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.8.2 |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☒ | ☐ | |

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 |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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). | ☐ | ☐ | ☒ | |
| 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) | ☐ | ☐ | ☒ | |

Comments:

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| **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 |
| 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:

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| **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:

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

Comments:

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|---|---|
| Name of the main author of the protocol: | Dominique Sighoko |
| Date: 09/30/2024 | |

| | | |
|---|---|---|
| Signature: |  | |

## ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

# Document Approval Record

| | |
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