NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Active Surveillance, Post-Authorization Study to Characterize the Safety of Tofacitinib in Patients with Moderately to Severely Active Ulcerative Colitis in the Real-World Setting Using Data from a US Administrative Healthcare Claims Database
Protocol number	A3921347
Protocol version identifier	1.0
Date	10 April 2020
EU Post Authorization Study (PAS) register number	Pending (prior to start of data collection)
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz® (tofacitinib)
Product reference	EU/1/17/1178/001-009, 014
Procedure number	EMEA/H/C/004214/X/0005/G
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	**Research Question**: What are the incidence rates of safety events of interest (described below) in adult ulcerative colitis (UC)

	patients treated with tofacitinib (including the immediate-release [5mg and 10mg twice daily] and the extended-release [11mg and 22mg once daily] formulations) in the course of routine clinical care? **Primary Objective**: To estimate the incidence rate of malignancy, excluding non-melanoma skin cancer (NMSC), in adult UC patients who initiate tofacitinib in the course of routine clinical care. **Secondary Objective**: To estimate the incidence rates of other safety endpoints of interest, including (but not limited to): NMSC, opportunistic infections (e.g. tuberculosis), major adverse cardiac events (MACE), venous thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]), hepatic events, serious infections, herpes zoster (HZ reactivation), progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, interstitial lung disease (ILD), surgery for UC, and death in adult UC patients who initiate tofacitinib in the course of routine clinical care. Incidence rates will be estimated among: <u>Cohort 1</u>: UC patients initiating tofacitinib, overall and stratified by dose (5mg vs. 10mg twice daily for the immediate-release formulation, and 11mg vs. 22mg for the extended release formulation) and prior biologic use. For contexualization and risk characterization purposes, incidence rates will also be estimated among the following groups:

	Cohort 2: UC patients who initiate biologics, overall and stratified by TNFi/non-TNFi use and number of previous biologic treatments Cohort 3: UC patients who initiate immunomodulators/immunosuppressants without concurrent biologics Cohort 4: UC patients naïve to both biologics and immunomodulators/immunosuppressants
Country(-ies) of study	United States
Author	[redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
MAH contact person	[redacted]

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
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EU	European Union
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
HR	Hazard ratio
Hx	History
HZ	Herpes zoster
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
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
OI	Opportunistic infection
PASS	Post-Authorization Safety Study
PE	Pulmonary embolism
PML	Progressive multifocal leukoencephalopathy
SAP	Statistical analysis plan
TB	Tuberculosis

Abbreviation	Definition
TNFi	Tumor necrosis factor inhibitor
UC	Ulcerative colitis
VTE	Venous thromboembolic events

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

4. ABSTRACT

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

- **Main author/affliation**: [redacted]

- **Rationale and background**: Tofacitinib, an inhibitor of the Janus kinase (JAK) family of kinases, was approved in the United States in May 2018 at a dose of 5mg twice daily or 10mg twice daily for the treatment of adults with moderate-to-severe ulcerative colitis (UC). In December 2019, the extended-release formulation was also approved for UC patients at a dose of 11mg once daily and 22mg once daily. Malignancy is a potential risk associated with the use of tofacitinib, and follow-up of large cohorts of patients over a long period is needed to evaluate risk of malignancy, as well as any other potential safety events of interest, that may be associated with tofacitinib treatment. Pfizer will implement a post-approval, active surveillance study of tofacitinib-exposed and unexposed patients using a United States (US) administrative healthcare claims database. This study is a post-marketing commitment to the US Food and Drug Administration (FDA).

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

- **Objectives**: 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.

  The secondary objective is to estimate the incidence rates of other safety events of interest, including (but not limited to) NMSC, opportunistic infections (e.g. tuberculosis), major adverse cardiac events (MACE), venous thromboembolic events (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE]), hepatic events, serious infections, herpes zoster (HZ) reactivation, progressive multifocal leukoencephalopathy (PML), gastrointestinal (GI) perforations, interstitial lung disease (ILD), surgery for UC and death in adult 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 an active surveillance study utilizing data from the International Business Machines (IBM) Watson Health MarketScan® Research Databases, a US administrative healthcare claims database.

- **Population**: The study 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 include baseline patient characteristics (i.e., clinical and demographic characteristics, comorbidities and current and past therapies). The primary outcome of interest is malignancy, excluding non-melanoma skin cancer (NMSC); other key safety events of interest include (but are not limited to) the following: NMSC, serious and opportunistic infections, hepatic events, venous thromboembolic and cardiovascular events, progressive multifocal leukoencephalopathy, gastrointestinal perforations, ILD, 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 will be included, with no upper limit on the sample size. Based on 2016-2018 Marketscan 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 and incidence rates of the safety events of interest described above in all study cohorts.

- **Milestones**:

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

5. AMENDMENTS AND UPDATES

None

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 EU PAS register	Pending (prior to start of data collection)
Final study report	30 May 2026

7. RATIONALE AND BACKGROUND

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

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 glucocortiocoids 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 5mg twice daily or 10mg twice daily for the treatment of adults with moderate-to-severe UC. In December 2019, the extended-release formulation was also approved for UC patients at a dose of 11mg once daily and 22mg once daily.

Malignancy is a potential risk associated with the use of tofacitinib, and follow up of large cohorts of patients over a long period is needed to evaluate risk of malignancy, as well as other 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 can help assess the risk of safety events of interest overall and within strata of disease severity, treatment history, and other concomitant therapy. The goal of this active surveillance study using data from the International Business Machines (IBM) Watson Health MarketScan® Research Databases is to assess the risk of malignancy and other safety events of interest in adult UC patients initiating treatment with tofacitinib. To

provide context for the findings, incidence rates of these events will also be estimated for adult UC patients treated with other approved systemic medications, as well as adult UC patients naïve to both biologics and immunomodulators/immunosuppressants.

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

8. RESEARCH QUESTION AND OBJECTIVES

The research question for this study is: What are the incidence rates of safety events of interest in adult ulcerative colitis (UC) patients treated with tofacitinib (including the immediate-release [5mg and 10mg twice daily] and the extended-release [11mg and 22mg 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:

- NMSC
- Serious infections
- Opportunistic infections (e.g. tuberculosis)
- Herpes zoster (HZ) reactivation
- Major adverse cardiac events (MACE)
- Venous thromboembolic events (VTE; deep venous thrombosis [DVT] and pulmonary embolism [PE])
- Hepatic events
- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Interstitial lung disease (ILD)
- 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 (5mg vs. 10mg twice daily, and 11mg vs. 22mg 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, 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, active surveillance, secondary data collection study of adult (aged 18 years or older) UC patients in the IBM Watson Health MarketScan® Research Databases.

Incidence rates and associated 95% confidence intervals (CIs) will be calculated in the four cohorts. 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

The active surveillance population includes 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 Section 9.3.2).

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

9.2.1.1. 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), tofacitinitb 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. Cohort 2 (Biologics cohort): Adult UC Patients Treated with Biologics

1. Initiation of biologic therapy (i.e. first prescription for a specifc 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 may also be on immunomodulators/immunosuppressants concurrently.

9.2.1.3. 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)

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

1. Naïve 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, details of which will be discussed in the SAP as mentioned above.

9.2.2. Exclusion criteria

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 and other variables, will be included in the SAP.

9.3.1. Baseline Data

Baseline data include, but are not restricted to, the following:

- 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 thromboembolic events,
    - history diabetes mellitus,
    - history of myocardial infarction [MI],
    - history of hypertension,
    - history of inherited coagulation disorders
- Concomitant use of immunomodulators/immunosuppressants at index date

- Use of the following medications within 12 months of index date:
    - oral steroids,
    - oral nonsteroidal anti-inflammatory drugs [NSAIDs],
    - antimicrobials,
    - anticoagulants,
    - beta blockers,
    - bisphosphonates,
    - narcotics,
    - proton pump inhibitors [PPIs]
    - statins

9.3.2. Follow-Up

Patients 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. 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, the occurences 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.

9.3.3. Endpoints of Interest

The endpoints of interest (to be defined via ICD-code based algorithms in the SAP) which will be captured in the interim and final study reports include the following:

- Malignancy, excluding non-melanoma skin cancer (NMSC
- NMSC
- Serious infections
- Opportunistic infections (e.g. tuberculosis)
- Herpes zoster (HZ) reactivation
- Major adverse cardiac events (MACE)
- Venous thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE])
- Hepatic events
- Progressive multifocal leukoencephalopathy (PML)
- Gastrointestinal (GI) perforations
- Interstitial lung disease (ILD)
- 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 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 from the start of data collection (30 June 2020) 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 59,080 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. 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.

For the safety endpoints of interest, descriptive statistics, counts and proportions, cumulative incidence proportions, and incidence rates (i.e., number of events per person-years) and associated two-sided 95% confidence intervals will be calculated as appropriate. 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 (5mg vs. 10mg, as well 11mg vs. 22mg for the extended-release formulation),
- Patient characteristics such as age at index date, including a subgroup analysis of patients <65 years vs. ≥65years

- VTE risk factors such as smoking status, history of hypertension and history of inherited coagulation disorders, and

- Key indicators of disease severity such as number of previous biologic treatments

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.

9.7.1. Interim Reports

Interim reports summarizing the incidence rates of safety events of interest will be provided as per the timeline in Section 6 (Milestones). These will provide 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.

9.7.2. Final Study Report

In the final study report, there will be some but limited flexibility to add additional endpoints and stratification, and it will contain populated tables in line with shells to be provided in the SAP.

In the final report, the tofacitinib cohort will be analyzed overall and stratified by patient age, dose (5mg vs. 10mg twice daily; 11mg vs. 22mg 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 monitor the safety of tofacitinib among US adult UC patients within the clinical practice setting utilizing 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. 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[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

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

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:

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

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

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8, 9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
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
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.1
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)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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

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:

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:

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))	☐	☒	☐	
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
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:

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:

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

Comments:

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

Comments:

Name of the main author of the protocol: [redacted]

Date: 10/04/2020

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

Not applicable