Study Protocol

Cohort Study of Long-term Safety of Upadacitinib for the Treatment of Ulcerative Colitis and Crohn's Disease in a Real-world Setting in Europe

Marketing Authorisation Holder: AbbVie Deutschland GmbH & Co. KG (EU), AbbVie Inc (USA)
Study number: P24-343

PASS Information

Title	Cohort Study of Long-term Safety of Upadacitinib for the Treatment of Ulcerative Colitis and Crohn's Disease in a Real-world Setting in Europe
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Joint PASS	No
Research question and objectives	This study aims to evaluate the long-term safety of upadacitinib use in adults in routine clinical care for the treatment of Ulcerative Colitis (UC) and Crohn's Disease (CD). All analyses will be conducted and presented for UC and CD combined and repeated for UC and CD separately. **Primary Objectives:** To describe and compare the incidence of gastrointestinal (GI) perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic inflammatory bowel disease (IBD) treatments at a similar line of therapy. To describe and compare, where possible, the incidence of fractures and drug-induced liver injury (DILI) in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of fractures and DILI. **Secondary Objectives:** To describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy: • Malignancy excluding non-melanoma skin cancer

	(NMSC), stratified by type • NMSC • Major adverse cardiovascular events • Venous thromboembolic event • Serious infections (defined as all infections that require hospitalization, including opportunistic infections) • Herpes zoster • Active tuberculosis • All-cause mortality Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes. In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program • Very elderly (aged ≥ 75 years) at the time of treatment initiation • Patients with moderate hepatic impairment at the time of treatment initiation • Patients with severe renal impairment at the time of treatment initiation • Patients with evidence of chronic infection with Hepatitis B virus or Hepatitis C virus at the time of treatment initiation
Country(-ies) of study	Denmark, Sweden, Spain
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Project Title: Cohort Study of Long-term Safety of Upadacitinib for the Treatment of Ulcerative Colitis and Crohn's Disease in a Real-world Setting in Europe

Principal Investigator: [redacted] on behalf of the entire study research team

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1. Table of Contents

2. List of Abbreviations

Abbreviations	Descriptions
AE	Adverse event
ATC	Anatomical Therapeutic Chemical classification
CD	Crohn's disease
CI	Confidence interval
DILI	Drug-induced liver injury
DMSc	Doctor of Medical Science
DSc	Doctor of Science
DVT	Deep vein thrombosis
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EMR	Electronic medical record
[redacted]	
EU	European Union
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GDPR	General Data Protection Regulation
[redacted]	
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practice
HBI	Harvey-Bradshaw Index
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
HZ	Herpes zoster
IBD	Inflammatory bowel disease
ICD-10	International Classification of Diseases, Tenth Edition
IEC	Independent Ethics Committee
IL	Interleukin
IR	Incidence Rate
IRB	Institutional Review Board
JAK	Janus kinase
MACE	Major adverse cardiovascular events
MAH	Marketing Authorisation Holder
MD	Doctor of Medicine
MI	Myocardial infarction
MPH	Master of Public Health
NMSC	Non-melanoma skin cancer
[redacted]	[redacted]
OI	Opportunistic infection
PAS	Post-authorisation studies
PASS	Post-authorisation safety study

[redacted]	[redacted]
PE	Pulmonary embolism
PhD	Doctor of Philosophy
PIN	Personal identity numbers
pMS	Partial Mayo Score
PPV	Positive predictive value
PS	Propensity Score
PY	Person-Year
RTI-HS	RTI Health Solutions
S1P	Sphingosine-1-phosphate
SAP	Statistical Analysis Plan
ScD	Doctor of Science
SMD	Standardized Mean Difference
[redacted]	
TB	Tuberculosis
TNF	Tumor necrosis factor
UC	Ulcerative colitis
USA	The United States of America
VTE	Venous thromboembolic event
WHO	World Health Organization

3. Responsible Parties

Parties	Name, Degree(s)	Title/Role	Affiliation	Address
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Co-investigator, SWIBREG	[redacted]	[redacted]	Clinical Epidemiology Division, Karolinska Institutet	
Coordinating investigators, Denmark	[redacted]	[redacted]	Department of Clinical Epidemiology, Aarhus University	
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4. Abstract

Title:

Cohort Study of Long-term Safety of Upadacitinib for the Treatment of Ulcerative Colitis and Crohn's Disease in a Real-world Setting in Europe

Version 1.0 04 July 2023

Main author: [redacted] Karolinska Institutet, Centre for Pharmacoepidemiology, KEP/CPE, Karolinska University Hospital Solna, T2:02, 171 76 Stockholm, Sweden

Rationale and background

Ulcerative colitis (UC) and Crohn's disease (CD) are immune-mediated chronic systemic inflammatory diseases grouped together as inflammatory bowel disease (IBD). Treatments of both disorders include therapeutic approaches targeting specific inflammation cascades. Upadacitinib is an oral selective and reversible *Janus kinase* (JAK) 1 inhibitor, approved for the treatment of adults (≥18 years of age) with moderate to severe UC or CD who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. The aim of the treatment is to use the lowest effective dose to maintain treatment response. Upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors. Although the upadacitinib clinical trials provide valuable information on the product's efficacy and safety, long-term safety data are needed for individuals who are exposed to upadacitinib. A prospective population-based cohort study of individuals in routine clinical practice will be conducted to investigate the incidence and occurrence of safety outcomes including gastrointestinal (GI) perforation, fractures, drug-induced liver injury (DILI), malignancy excluding non-melanoma skin cancer (NMSC) - stratified by type, NMSC, major adverse cardiovascular events (MACE), venous thromboembolic event (VTE), serious infections (defined as all infections that require hospitalization, including opportunistic infections [OI]), herpes zoster (HZ), active tuberculosis (TB) and all-cause mortality.

Research question and objectives

This study aims to evaluate the long-term safety of upadacitinib use in adults in routine clinical care for the treatment of UC and CD. All analyses will be conducted and presented for UC and CD combined and repeated for UC and CD separately.

Primary Objectives:

To describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy.

To describe and compare, where possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy.

Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for incidence comparison of fractures and DILI.

Secondary Objectives:

To describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy:

- Malignancy excluding NMSC, stratified by type
- NMSC
- MACE
- VTE
- Serious infections (defined as all infections that require hospitalization, including opportunistic infections)
- HZ
- Active TB
- All-cause mortality

Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes.

In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program:

- Very elderly (aged ≥ 75 years) at the time of treatment initiation
- Patients with of moderate hepatic impairment at the time of treatment initiation
- Patients with severe renal impairment at the time of treatment initiation
- Patients with evidence of chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) at the time of treatment initiation

Study design

The study is a long-term, non-interventional, cohort study that will be conducted using longitudinal secondary data collected from Denmark, Sweden and Spain, from authorization date of upadacitinib for the treatment of IBD until the end of 2032. A new-user, active comparator design will be used to address the objectives of the study. New user is defined as not having used that specific drug substance in the year (12 months, 365 days) before the first eligible treatment.

Each patient will be followed for each outcome of interest, from the date of the first upadacitinib treatment or select biologic IBD treatment (index date) to the end of the study period, study withdrawal (emigration in Denmark and Sweden, withdrawn from the registry or loss to follow-up in Spain), or death. Different upadacitinib cohorts depending on the line of treatment (number of previous targeted therapies for IBD) will be created.

Importantly, labelling changes following Article 20 procedure are likely to result in substantial differences in baseline characteristics of patients initiating upadacitinib and those initiating other systemic treatments. Therefore, initial in-depth descriptive analyses will be conducted to assess comparability across treatment cohorts and inform the design (including selection of suitable comparator/s) of subsequent analyses.

Population

The *study population* will be adult patients with IBD [redacted] in Denmark, [redacted] in Sweden, [redacted] in Spain, and who are new users of upadacitinib or select biologic IBD treatments. In Denmark and Sweden all individuals receiving a comparator treatment will be included, while in Spain a random sample of user matched on *line of treatment,* UC or CD, will be selected. Patients who used other JAK inhibitors before the *index date* will be excluded.

Variables

Exposure will be based on dispensed prescriptions and recorded treatment of either upadacitinib or select biologic IBD treatments. Currently approved select biologic IBD treatments (as of June 2023) include anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, golimumab), anti- interleukin (IL) antibodies (ustekinumab, risankizumab), and anti-alpha-4-beta-7 integrin antibody (vedolizumab). Additional upcoming biologic IBD treatments may be approved as the study progresses and included as potential comparator treatments. The primary outcomes will be GI perforation, bone fractures, and DILI. The secondary outcomes will be malignancy excluding NMSC (stratified by type), NMSC, MACE, VTE, serious infections, HZ, active TB and all-cause mortality.

Covariates such as age, sex, region of residency, disease characteristics and severity, comorbidities and previous and concomitant drug therapies will be retrieved and use to balance differences among exposure groups.

Data sources

In Denmark, [redacted] will be used. In Sweden, the [redacted] will be used.

In Spain, data collected from [redacted]

registry of patients with IBD, will be used. Because not all of the variables of interest are routinely collected in the [redacted]

Study size

The study size will depend on the market uptake of upadacitinib for UC and CD in Denmark, Sweden and Spain. All eligible patients exposed to upadacitinib identified through the data sources will be included, and no upper limit of the study size is defined. No hypotheses have been specified for testing as part of this study, and thus no formal power calculations have been conducted. For all outcomes except GI perforation the study objectives are to estimate and describe the incidences, comparative analyses should only be done if possible, therefore the study size assessment for this study will focus on the outcome GI perforation. The study size is estimated based on the probability that the upper limit of the confidence interval for the rate ratio stays below a level of concern. [redacted] Annually accrued patients will be monitored to assess yearly included number of patients.

Data analysis

Comparison of rates of GI perforation between upadacitinib and comparators will be made with a Cox regression model, by each *line of treatment* cohorts.

If assessed as feasible, based on (1) number of upadacitinib users, (2) number of other select biologic IBD treatments users suitable for comparison, and (3) number of safety events, Cox regression analyses will be performed to compare rates of DILI, bone fracture and all the secondary outcomes between upadacitinib and comparator treatments. Cox regression models will be performed separately for each outcome, stratified by *line of treatment*.

Comparative analyses of GI perforation will be performed in the interim report if number of patients is sufficient. Comparative analyses on all other outcomes will be performed in the final report, as applicable.

Milestones

AbbVie will initiate the study upon endorsement of the study protocol by the European Medicines Agency (EMA). An interim report of study results will be submitted to the EMA in Q4 2029, and the final study report will be submitted to the EMA in Q2 2035.

5. Amendments and Updates

This study (protocol number: P24-343), version 1.0, dated 04 July 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol P23-480, version 1.0, dated 03 October 2022, and will replace P23-480 in the risk management plan for upadacitinib

6. Milestones

Milestones	Planned Dates
Registration in the EU PAS Register	30 days post protocol approval
Start of data collection (date when data extraction starts for secondary data use)[1]	Q1 2025
Progress reports[2]	Annual, beginning Q4 2025 (except 2029)
End of data collection for interim report (date when interim analytical data set is available)[3]	Q4 2028
Interim report of study results[4]	Q4 2029
End of data collection for secondary data use (date when final analytical data set is available)	Q2 2034
Final report of study results	Q2 2035

[1] Start of data extraction will be determined by approval and availability of upadacitinib for UC or CD in each geographic region, with the planned date given being the date when data extraction is planned to start in Sweden. All data starting Q3 2022 will be collected and extracted at each data extraction through the entire study.
[2] First progress report will only include data from Sweden, see footnote [1] above. No progress report will be submitted during the year of interim report.
[3] Date when interim analytical data set is available will differ between the geographic regions, with the planned date given being the date when analytical data sets are available in all three regions.
[4] Interim report will include description of all planned study outcomes in the population under study. The GI perforation results in the interim report will include descriptive and comparative analyses in UC and CD separately, and in IBD combined.

7. Rationale and Background

Ulcerative colitis (UC) and Crohn's disease (CD) are immune-mediated chronic systemic inflammatory diseases grouped together as inflammatory bowel disease (IBD). Treatments of both disorders include therapeutic approaches targeting specific inflammation cascades [1].

Both UC and CD have a chronic relapsing-remitting course, characterized by abdominal pain, fever, and bloody or mucus-containing diarrhea, urgency, tenesmus and incontinence [2-4]. UC affects the large intestine and is characterized by diffuse and continuous inflammation and ulceration of mainly the innermost lining of the colon starting from the rectum [5-7]. In contrast, patients with CD have transmural skip lesions that affect any part of the gastrointestinal (GI) tract from the mouth to the perianal area [8]. The pathogenesis of IBD is multifactorial with largely unknown etiology where autoimmune, genetic, and environmental factors play a role [6, 7, 9, 10].

The incidence and prevalence of IBD is increasing worldwide and varies by country and region [11-13]. IBD prevalence varies by age group with peaks of onset between the ages of 15 and 30 years [14, 15]. The prevalence of UC varies between 161 and 294 per 100,000 in Denmark [16, 17], 198 per 100,000 in Sweden [17], and between 43.4 and 110 per 100,000 in Spain [17]. The UC

incidence rate has been reported to be 18.6 per 100,000 person-years (PYs) in Denmark, between 15.6 and 19 per 100,000 PYs in Sweden [12, 15, 18], and between 7.6 and 25.3 per 100,000 PYs in Spain [19, 20]. The prevalence of CD is 295 per 100,000 in Denmark [16], between 146 and 213 per 100,000 in Sweden [17], and between 19.8 and 87.5 per 100,000 in Spain [17]. CD incidence rate is 9.1 per 100,000 PYs in Denmark, between 9 and 12 per 100,000 PYs in Sweden [12, 15, 18], and 7.4 per 100,000 PYs in Spain [21].

IBD severity is assessed using disease activity indexes that take into consideration clinical presentation, extraintestinal manifestations, laboratory abnormalities, and endoscopic assessment [22, 23]. Patients with IBD can develop systemic symptoms like fever, weight loss and anemia. They may also present with extraintestinal manifestations including arthropathy, uveitis, erythema nodosum, primary sclerosing cholangitis, venous and arterial thromboembolism among others [24, 25]. Variability of affected areas, extraintestinal and systemic manifestations results in a spectrum of clinical presentations with different consequences [8]. Moderate to severe IBD is a debilitating condition with a significant physical, psychological, and economic burden [26, 27].

Though the majority of patients with IBD have a mild to moderate course, about 10% to 15% of patients experience an aggressive course with moderate to severe active disease [28, 29]. Without appropriate treatment, patients with IBD can have severe clinical symptoms that require physician visits, hospitalizations [30], surgeries [31, 32], and have a negative impact in quality of life.

Treatment is based on the extent and severity of disease activity, with the aim to control the symptoms and prevent long-term sequelae [28, 33, 34]. The induction treatment goal for patients with an active flare of IBD is to achieve remission, represented by mucosal healing and symptomatic control [33]. After clinical remission, the maintenance treatment goal is to prevent clinical and endoscopic relapse with appropriate treatment for long term use [35]. The choice of therapy is individualized, and the patient should be involved in the decision-making process. Among available treatments, selection of induction therapy depends on different factors, including patient preferences and characteristics, risk of adverse events (AEs), additional medications, patient history, availability of infusion centers, patient adherence, and costs. Maintenance treatment selection depends also on the treatment response to induction therapy [33, 36].

Medical treatments for UC / CD include systemic and locally acting aminosalicylates (albeit only recommended in UC), locally active steroids, systemic steroids, immunomodulators, and targeted therapies, such as biologic therapies (anti-tumour necrosis factor [TNF] agents, anti-integrins, or anti-interleukin [IL] antibodies) and small molecules (Janus kinase [JAK] inhibitors like tofacitinib, filgotinib, and upadacitinib) [35, 37, 38].

JAKs are part of the intracellular response mechanism to interleukins, interferons, and hormones such as erythropoietin, thrombopoietin, and growth hormone. Activation of the JAK signaling system is associated with inflammatory diseases and malignancies [39]. JAK inhibitors are a family of small molecules classified as immunomodulators that block JAK protein family members, including JAK1, JAK2, JAK3 and tyrosine kinase 2 [39, 40].

Upadacitinib is an oral selective and reversible JAK1 inhibitor, approved for the treatment of adults (≥18 years of age) with moderate to severe UC or CD who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent [41, 42]. The upadacitinib approved dose for induction in adult patients is 45 mg once daily for 8 weeks in UC and 12 weeks in CD. Maintenance doses are 15 mg or 30 mg once daily depending on age and risk factors for malignancy, cardiovascular disease and venous thromboembolism. The aim is to use the lowest effective dose to maintain treatment response [43]. In addition, upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors.

Upadacitinib was developed to achieve greater JAK1 selectivity over JAK2, JAK3, and tyrosine kinase 2, resulting in a more favorable benefit-risk profile than other currently approved JAK inhibitors. Potential safety risks have been identified for JAK inhibitors, including malignancy excluding non-melanoma skin cancer (NMSC), NMSC, major adverse cardiovascular event (MACE), venous thromboembolic event (VTE), serious infection including opportunistic infection (OI), active tuberculosis (TB), herpes zoster (HZ), drug-induced liver injury (DILI), bone fracture, GI perforation, and all-cause mortality. Because of small sample sizes, restrictive inclusion and exclusion criteria, and short follow-up, evaluations of safety data based on results from upadacitinib clinical trials are limited and there is a need to complement them with data from studies in a real-world setting [44]. From a clinical and safety perspective, it is important to gain knowledge of these and other safety concerns for upadacitinib, and to provide comparisons with other relevant treatment alternatives for UC and CD.

This post-authorization safety study (PASS) is a commitment to the European Medicines Agency (EMA), which is designed to characterize the long-term safety of upadacitinib use in adult patients with moderate to severe UC or CD in real-world settings and to evaluate the important identified and potential risks as described in the Risk Management Plan in Denmark, Sweden and Spain. Rates of these events will be described to better understand safety in populations with limited or missing information from the clinical development program.

8. Research Question and Objectives

This study aims to evaluate the long-term safety of upadacitinib use in adults in routine clinical care for the treatment of UC and CD. All analyses will be conducted and presented for UC and CD combined and repeated for UC and CD separately.

Primary Objectives:

To describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy.

To describe and compare, where possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a

similar line of therapy.

[redacted]

Secondary Objectives:

To describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy:

- Malignancy excluding NMSC, stratified by type
- NMSC
- MACE
- VTE
- Serious infections including OI (defined as infections that require hospitalization)
- HZ
- Active TB
- All-cause mortality

[redacted]

In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing).

When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program

- Very elderly (aged ≥ 75 years) at the time of treatment initiation
- Patients with moderate hepatic impairment at the time of treatment initiation
- Patients with severe renal impairment at the time of treatment initiation
- Patients with evidence of chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) at the time of treatment initiation

9. Research Methods

9.1. Study Design

The study is a long-term, non-interventional, register-based, cohort study of adults with UC or CD exposed to upadacitinib or select biologic IBD treatments. An active comparator, new user cohort study design will be utilized.

The study will be conducted using longitudinal secondary data collected from Denmark, Sweden and Spain.

In Denmark, [redacted] covering populations of approximately 5.8 million people will be used.

In Sweden, the [redacted] and the Swedish [redacted] covering populations of approximately [redacted] will be used.

In Spain, data collected from the [redacted]

Details about the data sources are provided in Section 9.4.

Select biologic IBD treatments, evaluated as potential comparator treatments, approved in the European Union (EU) for UC or CD as of June 2023 include anti-TNFα agents (infliximab, adalimumab, golimumab), anti-IL antibodies (ustekinumab, risankizumab), and anti-alpha-4-beta-7 integrin antibodies (vedolizumab) [8, 45]. Additional upcoming biologic IBD treatments may be approved as the study progresses and included as potential comparator treatments. Anatomical Therapeutic Chemical classification (ATC) codes and procedure codes for the current approved select biologic IBD treatments are listed in Table 9 in Annex 3. Additional Information. Other advanced therapies with newly approved mechanism of action e.g., Sphingosine-1-phosphate (S1P) agonists may become relevant as comparator treatments as the study progresses, depending on the development within clinical practice and future use of different treatments.

Importantly, labelling changes following Article 20 procedure are likely to result in substantial differences in baseline characteristics of patients initiating upadacitinib and those initiating biologic IBD treatments. Specifically, patients initiating upadacitinib may differ in age, in cardiovascular risk profile and in malignancy risk profile. Therefore, in-depth descriptive analyses will be conducted to assess comparability across treatment cohorts and inform the design (including selection of suitable comparator/s) and conduct of subsequent analyses of the safety outcomes.

A *new user* study design will be used to address the objectives of the study. A *new user* is defined as a patient not having used that specific drug substance in the year (12 months, 365 days) before initiating the first treatment in the study period (see definition in Section 9.2.3.). The date of the first upadacitinib treatment or select biologic IBD treatments within the study period (see definition in Section 9.2.3.) will be defined as the *index date*.

Upadacitinib in patients with UC or CD can be administered in clinical practice at different lines of

treatment. Since the line of treatment to some extent reflects the disease course, which in turn can modify the risk of the outcomes of interest, it is important to take line of treatment into consideration when presenting and analyzing data from a real-world setting. *Line of treatment* will be defined as the number of previous advanced therapies for IBD before the *index date*. Different upadacitinib cohorts depending on *line of treatment* will be created. In Spain, for each upadacitinib cohort, eligible patients initiating a select biologic IBD treatment will be matched by *line of treatment* and IBD diagnosis (UC or CD) and, if feasible, by age and sex, to create a comparator cohort to each upadacitinib cohort. [redacted] the comparator cohorts in Spain need to be restricted to a limited random sample of patients initiating select biologic IBD treatments. In Denmark and Sweden, all patients initiating a select biologic IBD treatment will be included in the comparator cohorts according to the *line of treatment,* no selection or matching ratio will be applied.

All analyses will be conducted and presented separately for each country and for UC and CD combined as well as repeated for UC and CD separately, if sample size allows.

9.2. Setting

9.2.1. Study Population

[redacted]

The *study population* will comprise eligible patients from the *source population* meeting the following **inclusion criteria**:

- Be a *new user* (see definition in Section 9.1.) of either upadacitinib or one of the select biologic IBD treatments i.e. have at least one *index date*
  - All upadacitinib-exposed patients meeting inclusion and exclusion criteria will be included in the study in the 3 participating countries
  - In Denmark and Sweden, all patients initiating a select biologic IBD treatment meeting the inclusion and exclusion criteria will be included in the study
  - In Spain, a random sample of users of the select biologic IBD treatments will be selected for each upadacitinib-exposed patient, matched on *line of treatment* and IBD diagnosis (UC or CD) and, if feasible, by age and sex
- Have a diagnosis of either UC or CD before or at the *index date*
  - have one UC or CD diagnosis in [redacted]
  - have one UC or CD diagnosis in [redacted]
  - have two consecutive diagnoses of UC at different dates and at least the last within 12 months before the *index date* as registered in [redacted] Denmark and Sweden or
  - have two consecutive diagnoses of CD at different dates and at least the last within 12 months before the *index date* as registered in [redacted] Denmark and Sweden

- Be ≥ 18 years old at the *index date*
- For Denmark and Sweden: Have at least 12 months' continuous residency in the respective country prior to the *index date*.
- For Spain: The appropriateness of requiring a minimum period of prospective data collected in [redacted] record before the *index date*, will be assessed during the pilot phase [redacted] This criterion aims to ensure that information on the prevalence of risk factors for the study outcomes is available [redacted]

There is overlap and similarities in the clinical presentation of different IBD subtypes. For this reason, the same patient may be diagnosed with more than one IBD subtype during follow-up, in particular at the beginning of the disease. To minimize misclassification, at least two UC diagnostic codes will be required [redacted] before index date [redacted]

Patients classified as CD according to the definition above in the NPRs in Denmark and Sweden, may be classified as having another IBD subtype (i.e., UC) over time, as additional diagnostic procedures and clinical evolution may provide information that motivates this. For this reason, the IBD subtype definition listed in the inclusion criteria above will allow patients to be included as having different subtypes for different drug exposures (e.g., a patient might be classified as having UC when being exposed to infliximab, but because the patient developed perianal fistula and because granulomas where present in the pathology report of the second control colonoscopy the patient was reclassified as having CD before being exposed to upadacitinib).

In the [redacted], if a patient has his/her IBD diagnosis updated during the study conduct, the patient will be considered to have had the latest diagnosis for the entirety of the study period.

The following **exclusion criteria** apply to the study population:

- Patients who used other JAK inhibitors (e.g., tofacitinib, filgotinib) at any time (all available lookback time) before the *index date* will be excluded
- Patients with a concomitant dispensation of two or more study treatments on the same date will be excluded

9.2.2. Treatment cohorts

The treatment cohorts in the study will be:

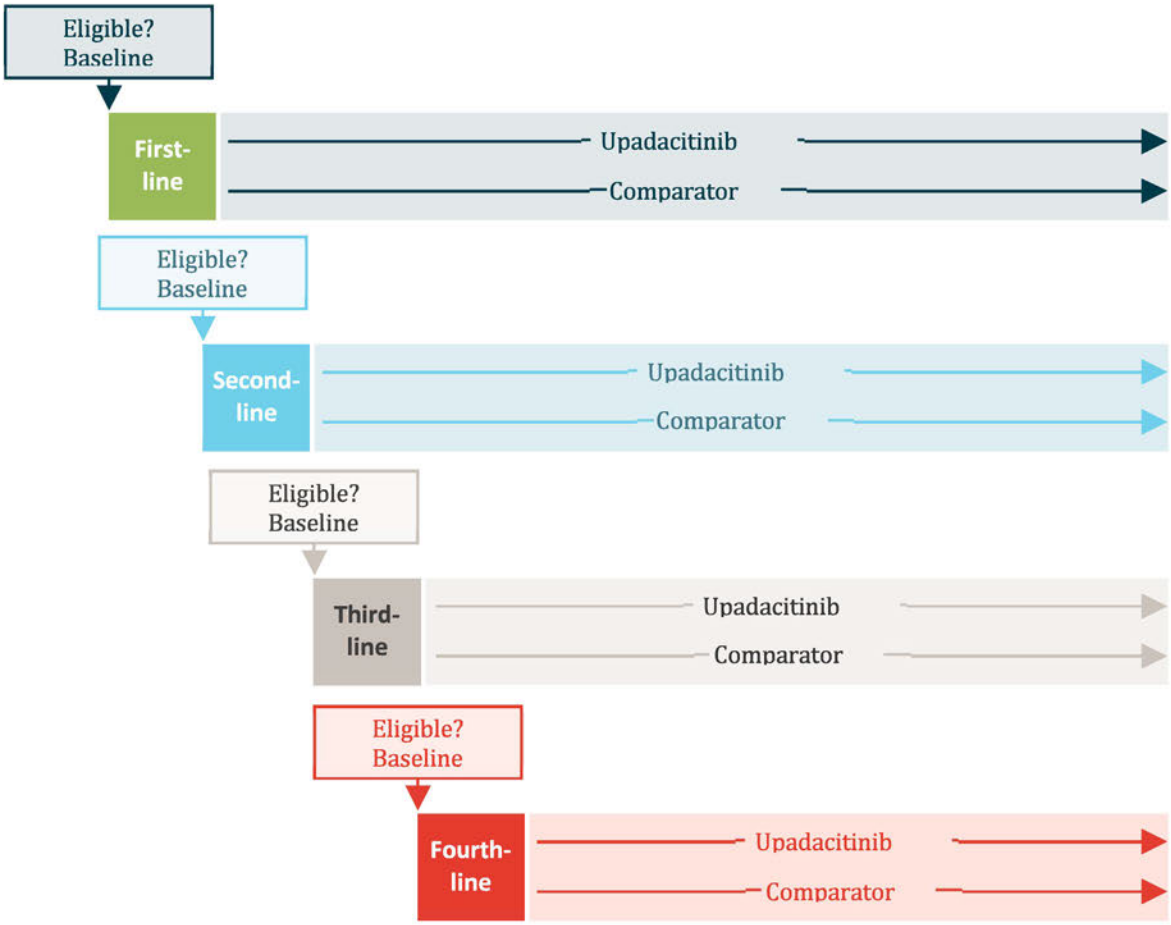
- Upadacitinib cohorts
- Comparator cohorts including select biologic IBD treatments

Different upadacitinib cohorts depending on *line of treatment* will be created. Patients can contribute person-time to several cohorts, if eligible. However, a patient can only contribute to

one cohort within a given *line of treatment.* For each cohort (the upadacitinib cohorts and the comparator cohorts), *index date* will be the time of initiation of the new treatment that is specific to that cohort. At each *index date* for a patient, the inclusion criteria listed above will be applied, baseline variables extracted and *line of treatment* assigned.

In Spain, for each upadacitinib cohort, eligible patients initiating a select biologic IBD treatments will be matched by *line of treatment* and IBD diagnosis (UC or CD) and, if feasible, by age and sex, to create a comparator cohort to each upadacitinib cohort. A ratio of one upadacitinib user to two comparators will be used if feasible. However, the actual matching ratio that can be achieved will depend on the number of upadacitinib users. In Denmark and Sweden, all patients initiating select biologic IBD treatments will be included in the comparator cohorts according to the *line of treatment,* no selection or matching ratio will be applied.

Figure 1 Cohorts creation by *line of treatment*



9.2.3. Study Period

The *study period* will start at first authorization date of upadacitinib for the treatment of UC in Denmark and Sweden (25 July 2022) and on the date upadacitinib is approved for reimbursement for the indication of UC in Spain. The study period will end 31 December 2032 in all countries.

Patients using one of the treatments under study will be included through the whole *study period*. To allow for at least 5 years of follow-up time for the malignancy outcomes, the population will be restricted to patients included up until 31 December 2027, when analyzing these. The study period may be shortened if the number of upadacitinib users exceeds the expectations or extended otherwise.

9.2.4. Follow-Up

Each patient will be followed specifically for each outcome of interest, from the *index date* for a certain exposure to the end of the *study period*, study withdrawal (emigration in Denmark and Sweden, withdrawn from the registry or loss to follow-up in Spain), or death. Further censoring of the time at risk is described in Table 2 in Section 9.3.1.

9.3. Variables

9.3.1. Exposure

Exposure will be based on dispensed prescriptions and recorded treatment of either upadacitinib or select biologic IBD treatments. Upadacitinib dose regimen is a daily induction dose of 45 mg for 8 weeks and 12 weeks, for patients with moderate to severe UC and CD, respectively. For UC, the daily induction dose can be continued for another 8 weeks if needed, for adequate treatment response. For CD, induction treatment can be prolonged with a daily dose of 30 mg for another 12 weeks, if needed. The maintenance dose of upadacitinib is 15 mg or 30 mg once daily in patients with UC and CD. Upadacitinib 15 mg should be used for treatment of elderly patients ≥ 65 years of age or patients with risk factors for malignancy, MACE or VTE. Currently approved select biologic IBD treatments (as of June 2023) and their dose regimens are listed in Table 1. Additional upcoming biologic IBD treatments may be approved as the study progresses and included as potential comparator treatments. Other advanced therapies with new mechanism of action, e.g., S1P agonists, may become relevant as comparator treatments as the study progresses, depending on the development within clinical practice and future use of different treatments.

Table 1 List of biologics approved for the treatment of adults with UC or CD as of June 2023

Biologic / Biosimilar	ATC code	Induction treatment	Maintenance treatment
anti-TNFα agents			
Adalimumab	L04AB04	UC and CD: Subcutaneous Week zero – 160 mg once Week two – 80 mg once	UC and CD: Subcutaneous Week four – 40 mg Every other week – 40 mg
Infliximab	L04AB02	UC and CD: Intravenous Week zero – 5 mg/kg Week two – 5 mg/kg Week six – 5 mg/kg	UC and CD: Intravenous Ever eight weeks – 5 mg/kg Subcutaneous (Spain only): Every 2 weeks- 120 mg after 2 intravenous infusions
Golimumab	L04AB06	UC: Subcutaneous Week zero – 200 mg Week two – 100 mg	UC: Subcutaneous, weight-based Every 4 weeks – 100 mg, ≥ 80 kg – 50 mg, < 80 kg
anti-IL antibodies			
Ustekinumab	L04AC05	UC and CD: Intravenous Weekly weight-based dose, according to description provided in section Dosage in the Summary of Product Characteristics	UC and CD: Subcutaneous 90 mg at Week 8 after the intravenous dose, then every 12 weeks.
Risankizumab	L04AC18	CD: Intravenous Week zero – 600 mg Week four – 600 mg Week eight – 600 mg	CD: Subcutaneous 360 mg at Week 12 after the intravenous dose, then every 8 weeks.
anti-alpha-4-beta-7 integrin antibodies			
Vedolizumab	L04AB33	UC and CD: Intravenous Week zero – 300 mg Week two – 300 mg Week six – 300 mg	UC and CD: Intravenous Every 8 weeks – 300 mg Subcutaneous Every 2 weeks – 108 mg after at least 2 intravenous infusions.

In Denmark, exposure will be identified by joining information from the [redacted] procedure codes from the Danish NPR and dispensed prescriptions from the [redacted] the start date is the date of dispensation of the prescription. In the Danish

[redacted] the start date is the date of procedure and in [redacted] it is date of administration.

In Sweden, an algorithm to identify exposure using joint information from [redacted] and [redacted] will be used which will be defined in the Statistical Analysis Plan (SAP) [50, 51]. In [redacted] start date of exposure is registered by the physician while in the [redacted] the start date is the date of dispensation of the prescription. In the [redacted] the start date is considered the start date of the visit that the treatment administration is associated with.

In Spain, exposure will be identified in the [redacted] registry through pre-defined treatment-specific data fields. Data on IBD treatments are considered mandatory variables in the [redacted] which permits capture of time-dependent information about exposure to the study treatments. Specific exposure variables of interest include: date of initiation and date(s) of any dose changes; dose (at induction, maintenance); discontinuation date and reason for discontinuation.

The first start date of upadacitinib or one of the comparator treatments within the *study period* (see definition in Section 9.2.3.) will be defined as the *index date*. Patients who switch from a select biologic IBD treatment to upadacitinib and between drugs among the select biologic IBD treatments may be eligible to re-enter the study with a new *index date* and new baseline assessment. In Spain, these patients will be newly matched with appropriate patients with the same *line of treatment*.

Continuous exposure will be defined based on the first and subsequent dispensed prescriptions and recorded treatment, considering the available information in each country. Each dispensation/recorded treatment will be assumed to last for a prespecified number of days (to be defined in the SAP), unless there is a recording of a stop date in the data sources. If there is a stop date recorded in one of the data sources then exposure discontinuation will be defined by the stop date and duration of exposure will be defined as the stop date minus the start date. For dispensations/recorded treatments without a recorded stop date exposure discontinuation will be defined once more than a prespecified number of days (to be defined in the SAP) have elapsed after the end of a given dispensation/recorded treatment. Dispensation/record of a new treatment while continuously exposed to a previous treatment will be regarded as a switch of treatment. The previous treatment will be considered discontinued at the time of initiating subsequent treatment, i.e., all changes will be considered switching and therefore no overlap between different exposure groups will be assessed.

To approximate the dose of upadacitinib taken in Denmark and Sweden, strengths of upadacitinib dispensed (45mg, 30 mg and 15mg) will be used, assuming the intake is equal to one tablet a day.

Exposure definitions that will be used are presented in the following table. Additional information about which definition is used for each outcome is provided in Section 9.7.1.

Table 2 Exposure definitions

Exposure definition	Description
Ever-treated	Patients will be considered exposed from *index date* until the first occurrence of the specific outcome being analysed or end of follow-up, regardless of treatment switch or discontinuation.
On-treatment	Patients will be considered exposed from *index date* until first occurrence of the specific outcome being analysed, end of follow-up, treatment discontinuation, or treatment switch to other study treatment or other JAK inhibitor.

9.3.2. Outcomes

The primary and secondary study outcomes are described in Table 3.

In Denmark and Sweden, International Classification of Diseases, Tenth Edition (ICD-10) code-based algorithms will be used to identify outcomes from the National Registries.

In Spain, outcomes will be ascertained using data on diagnoses, procedures, medical product recorded information, and information collected in the [redacted], according to availability.

Only first events after *index date* will qualify as outcomes. Patients with prior history of any of the outcomes of interest will not be excluded from the study. Additional information on the outcomes are listed in Table 10 and Table 11 in Annex 3. Additional Information.

Table 3 Study Outcomes and Data Sources

	Denmark	Spain	Sweden
Primary outcomes			
GI perforation	[redacted]		
Bone fracture			
DILI			
Secondary outcomes			
Malignancy excluding NMSC Malignancy by type	[redacted]		
NMSC			

MACE (non-fatal myocardial infarction [MI], non-fatal stroke, and cardiovascular disease related death [52])	[redacted]
VTE (including deep vein thrombosis [DVT] and pulmonary embolism [PE])	
Serious infections including OI (defined as infections that require hospitalization [53-56])	
TB	
HZ	
All-cause mortality	

Lag-time for malignancy excluding NMSC and NMSC

For malignancy excluding NMSC and NMSC, exposure person-time and time to event will be started to be counted from the lag-time of 12 months after *index date*. Events occurring during the 12 months of lag time will not be considered as study outcomes for the main analysis. Sensitivity analyses with 0 and 6 months of lag time will be conducted.

Since the time between exposure and malignancy development and diagnosis commonly has a long latency, the association is susceptible to preexistence of the malignancy before the exposure and protopathic bias (reverse causality) [58-60]. Therefore, to evaluate the association between the exposure and malignancy outcomes, a 12-month lag-time period after *index date* will be considered. This means that malignancy events occurring within this lag-time will be excluded and will not be considered as outcomes. The lag-time of 12 months can be considered free of protopathic bias according to simulation studies [61].

9.3.3. Baseline Variables, Possible Confounders and Effect Modifiers

In addition to exposures and outcomes, other relevant characteristics that are captured in the [redacted] will be collected and assessed in this study. These variables will include demographic and socioeconomic measures (e.g., age, sex, region of residence, education), proxy measures for lifestyle factors (e.g., smoking, alcohol use), comorbidities and medical history, relevant risk factors for study outcomes, past and concurrent medication use, common extraintestinal manifestations, proxies of extent and localization of the IBD, and healthcare utilization as proxies of severity.

In Sweden, variables [redacted] might be included as well, depending on the coverage and quality of the reporting at time of the study. IBD activity/severity is usually measured with disease activity scores like the Mayo Score in UC and the Harvey-Bradshaw Index in CD. IBD activity

according to [redacted] may have a high proportion of missing information (overall 57%, from 8% to 99% by region) according to [redacted] annual report [redacted]. For these reasons and in concordance with previous studies, proxies will be used to measure UC and CD activity and severity: *line of treatment*, IBD related surgery, IBD hospitalizations, and steroid use.

In Spain a reduced set of variables obtain [redacted] may be provided in the SAP according to availability and feasibility. Additional details according to data sources for each variable classified by [redacted] review are presented in Table 12 in Annex 3. Additional Information.

A list of potential measured confounding factors and effect modifiers are presented in Table 4. In general, a one-year look-back period prior to *index date* will be used for medication use and disease severity proxies and five years for all the other variables.

Final codes and details of baseline variables, potential confounders and effect modifiers will be described in the SAP.

Table 4 Potential Confounders and Effect Modifiers

Data type	Description
Demographics	Age Sex Education Region of residency
Lifestyle factors	Smoking (identified through proxies) Alcohol use (identified through proxies)
Comorbidities	Charlson's Comorbidity Index components, as available [62-65] (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor without metastasis, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, AIDS) Cardiovascular risk factors [66] (age, sex, smoking identified through proxies, obesity, hypertension, hyperlipidemia, diabetes, previous cardiovascular or cerebrovascular events, coronary artery procedures) Atrial fibrillation Diverticulosis / diverticulitis Osteoporosis Renal impairment Hepatic disease / Moderate hepatic impairment HBV / HCV

IBD Common extraintestinal manifestations [67]	Musculoskeletal (arthritis, ankylosing spondylitis, sacroiliitis) Skin and mouth (erythema nodosum, pyoderma gangrenosum, fissures and fistulas, vitiligo, psoriasis, amyloidosis) Hepatobiliary (sclerosing cholangitis, cholelithiasis) Ocular (uveitis, iritis, episcleritis) Anemia
IBD Treatment History	Concomitant medication (immunomodulators, 5-aminosalicylic acid, corticosteroids) Biologic treatment naive Prior biologic therapies, any and number Prior non-biologic therapies (immunomodulators, 5-aminosalicylic acid, corticosteroids), and number of steroid courses
Extent and localization of IBD [68]	IBD duration ICD codes assigned for phenotypes of the Montreal Classification in combination with the Montreal Classification from SWIBREG (Sweden only): CD location (ileal, colonic, ileocolonic or location not defined) CD Behaviour (non-stricturing and non-penetrating, stricturing, penetrating, perianal disease) UC extent (proctitis, left-sided colitis, extensive colitis, extent not defined)
IBD severity (Spain only)	IBD severity – Date of severity assessment – Partial Mayo score (pMS) and components of pMS (UC only) – Harvey-Bradshaw Index (HBI) and components of HBI (CD only) – Stools/day – Blood in stools – Nocturnal stools – Other severity variables faecal calprotectin, C-reactive protein, haemoglobin (not in all patients but in a great proportion, at least once per year)
Healthcare utilization as proxies of IBD severity prior to *index date* (Denmark and Sweden only)	Number of IBD inpatient days per year Number of IBD outpatient visits per year Number of non-IBD inpatient days per year Number of non-IBD outpatient visits per year Acute IBD-surgery
Medication use within 1 year prior to *index date*	Antimicrobials Anticoagulants Bisphosphonates Iron Antihypertensives Lipid-lowering drugs Oral hormonal therapy and contraceptives

Previous history of outcomes	DILI Bone fracture GI perforation Malignancy (excluding NMSC) NMSC MACE (non-fatal MI, non-fatal stroke [83]) VTE (including DVT and PE) Serious infections (defined as infections that require hospitalization, including OI [84-87]) TB HZ
VTE risk factors [69, 70]	Previous VTE Major or traumatology surgery Heart failure Oral hormonal therapy and hormonal contraceptives Malignancy Inherited hypercoagulable disorders Acquired hypercoagulable disorders Inpatient care Obesity *Other VTE risk factors such as immobilization cannot be adequately captured within using the patient registry.

9.4. Data Sources

9.4.1. Denmark and Sweden

In Denmark, data from the following [redacted] will be used, [redacted] register, and the [redacted]. The [redacted] in Denmark will be used to define exposure, outcomes, and study variables to conduct this long-term safety study of upadacitinib in the treatment of UC and CD in Denmark.

In Sweden, data from the quality [redacted] will be used as well as data from the following [redacted]

Sweden and also with disease severity, as the register in recent years has focused on recording patients exposed to biological treatments [71]. [redacted] will be used to define exposure, outcomes, and study variables to conduct this long-term safety study of upadacitinib in the treatment of UC and CD in Sweden [72].

The assignment of [redacted] residents at [redacted] within each country [73-75]. The [redacted] so individuals can be followed-up throughout their lifetime, except for migrants. The [redacted] are updated on a yearly basis with up to two years of production time before released for research, depending on the content. The [redacted] contain the following information:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted] 5.8 million). The coverage and quality [redacted] have been well established in the literature [77]. Due to the breadth of capture of clinical outcomes across providers as well as "cradle to grave" longitudinal coverage, these registries have been successfully utilized for numerous post-marketing safety studies. Based on these attributes as well

as estimates of UC and CD prevalence and expected uptake of upadacitinib, the [redacted] in Denmark and Sweden are expected to provide statistically relevant numbers of upadacitinib and comparator treated individuals within the projected study timelines as well as long and complete follow-up time for long-latency outcomes of interest.

Table 5 Data Sources in Denmark and Sweden

[redacted]

9.4.2. Spain

Spain, a country with a population of 47 million, has a national health service that provides universal tax-funded healthcare to all Spanish residents. Specialist care is provided in specialist care centres and hospitals in the form of outpatient and inpatient care.

[redacted]

(e.g., age, IBD diagnosis, immunomodulator and biologic therapy start/stop dates, any bowel surgery) on the eCRF, while completion of other fields is optional. Determination regarding the research quality of [redacted] is made based on the percentage of patients within a site who are considered "complete" based on predefined critical variables. To be considered complete, the following variables cannot be missing: date of birth, sex, date of diagnosis, actual diagnosis, date of inclusion, date of last appointment, disease location, IBD surgical procedures, and use of immunosuppressants and biologic therapies.

[redacted]

Investigators are interested and will be available to conduct this study.

9.5. Study Size

The study size will depend on the market uptake of upadacitinib for UC and CD in Denmark, Sweden and Spain. All eligible patients exposed to upadacitinib identified through the data sources will be included, and no upper limit of the study size is defined. No hypotheses have been specified for testing as part of this study, and thus no formal power calculations have been conducted. For all outcomes except GI perforation the study objectives are to estimate and describe the incidences, comparative analyses will only be done if possible, therefore the study size assessment for this study will focus on the outcome GI perforation.

[redacted]

Based on the above assumptions and the formula recommended by Rothman and Greenland [99, 100] the sample size needed, for the upper limit of the CI for the rate ratio to be under the defined limits of concern with 90% probability for GI perforation, will be estimated. The formula for calculating the PYs in the upadacitinib cohort is as follows:

$$N = \frac{(Z' + Z)^2[RI_0 + I_1]}{RI_1I_0[ln(F)]^2}$$

Z = the value from the standard normal distribution corresponding to the level of confidence=1.96 for 95% confidence intervals

Z′ = the value of the cumulative normal distribution that corresponds to the desired probability that the upper confidence limit is below the defined limit of concern = 1.282 for 90% probability

R = relative size of comparator and upadacitinib = 2 for a 1:2 ratio

I_0 = incidence rate per PY among comparators = 0.62

I_1 = incidence rate per PY among upadacitinib = the same as for comparator under the assumption of no effect difference

F = the defined limit of concern for the upper limit of the CI [redacted]

Table 6 expresses the study size (PYs) for upadacitinib and the number of individuals needed to be included, for the upper limit of the CI for the rate ratio of GI perforation to be under the defined limits of concern with 90% probability.

Table 6 PYs for upadacitinib and number of individuals needed to be included for the upper limit of the CI for the rate ratio of GI perforation to be under the defined limits of concern with 90% probability

[redacted]

9.6. Data Management

Data retrieval and management will be conducted separately in each country. The coordinating investigator in each country will obtain all necessary permissions and prepare a data application to its country-specific data custodian.

[redacted]

[redacted]
only members of the research team in charge of the data management and analysis will have access to the data.

In Spain, the [redacted] protected MySQL database, which is maintained on a server in a secure facility. Data will be accessed by RTI Health Solutions (RTI-HS) according to the [redacted] standard practice. RTI-HS will log on to the [redacted] secure server, download the data files, and store the data in a secure server in Barcelona, Spain, with backups in the EU. Only selected RTI-HS personnel in Barcelona will have data access. Once the data are received, RTI-HS will develop a data dictionary using SAS statistical software. The data dictionary will document any data transformations applied to the received data sets in order to create the analytic data sets. The data dictionary will include variable names, formats, and any SAS code used to create derived variables from raw variables.

The transfers of data from the [redacted] may include data for patients who do not qualify for the analytic purposes of the present study; however, these data may be used to determine whether the analytic database is representative of the [redacted] data overall. All data received from the registry will be covered by the informed consent form signed by all patients at enrolment in the [redacted]. Data not used for the analysis will be filtered out by RTI-HS. Only data essential to the planned analyses will be retained in the analytic database.

A separate database will be created for the medical record data collected via the electronic questionnaire, the details of which will appear in a stand-alone Data Management Procedures manual. This manual will also include procedures for contacting sites for chart review and will describe the flow of abstracted clinical data into the study database. The manual will also include the chart abstraction instrument, which will be piloted during the first phase of the study.

In all countries, data will be cleaned and coded, and harmonized analytic datasets will be prepared according to the specifications provided in the SAP and internal standard operating procedures of each research partner. Full audit trail, starting from raw data obtained from register holders and ending with the creation of statistical tables and graphs in reports, will be maintained.

Data cleaning, verification of the raw data, and data analysis will be performed in each country and only aggregated data will be combined and delivered to the principal investigator and the marketing authorisation holder (MAH). The statistical software packages STATA, R, and SAS 9.4 or later (SAS Institute Inc., Cary, North Carolina, USA) will be used for data management and analyses.

9.7. Data Analysis

This section outlines the analytical plans to address the study objectives. The final analytic

approach will be described in a stand-alone SAP, which will be completed before any comparative analyses are performed. All analyses will be conducted and presented separately for each country and for UC and CD combined as well as for UC and CD separately, if sample size allows. Descriptive analyses will be performed in the interim report and the final report. Comparative analyses of GI perforation will be performed in the interim report if number of patients is sufficient. Comparative analyses on all other outcomes will be performed in the final report, as applicable.

The labeling updates due to the Article 20 procedure pose three distinct challenges for the long-term safety study. First, patients who have risk factors for MACE, malignancy and VTE at baseline and who are treated with upadacitinib could be those with "no other treatment options" based on Warnings and Precautions of the SmPC, likely leaving the upadacitinib exposed cohort with no suitable treatment comparators. This could also be true for those without risk factors. Second, among those at higher risk at baseline, patients prescribed upadacitinib will be more likely to have failed other treatments, not responded to lower dose of upadacitinib, and have higher burden of disease compared with patients prescribed other treatments. These patients may also be at high risk for safety outcomes due to disease activity or exposure to numerous prior treatments. Lastly, among those at low risk at baseline, patients prescribed upadacitinib will also be more likely to have failed other therapies, and have higher disease burden compared with patients prescribed other treatments. The anticipated lower incidence of safety outcomes in patients with lower risk raises additional feasibility concerns. To address these challenges, different cohorts depending on *line of treatment* will be created. In addition, an assessment of comparability of users of upadacitinib and select biologic IBD treatments will be conducted through in-depth assessments of treatment pattern utilization and patient disposition at baseline (see Section 9.7.2.).

9.7.1. Exposure definition per outcome

For the analysis, an outcome can be classified as an acute onset outcome and/or a delayed onset outcome. Table 7 below presents the classification per outcome (described in Section 9.3.2.) together with the exposure definition (described in Section 9.3.1.) that will be used for the primary analysis and as potential sensitivity analysis.

- Acute onset outcomes: Generally, these events might be triggered during or soon after drug treatment
- Delayed onset outcomes: Generally, these events take time to develop and be reported. These would occur after a long-term drug treatment and might even occur months or years after the treatment has been stopped

For outcomes classified as delayed onset outcomes, the *ever-treated* exposure definition will be used as primary analytical approach. With the *ever-treated* definition, patients will be considered exposed from *index date* until the first occurrence of the specific outcome being analysed or end of *follow-up,* regardless of treatment switch or discontinuation.

For outcomes classified as acute onset outcomes, the *on-treatment* exposure definition will be

used as primary analytical approach. With the *on-treatment* definition, patients will be considered exposed from *index date* until first occurrence of the specific outcome being analysed, *end of follow-up*, treatment discontinuation, switching to another study treatment or another JAK inhibitor.

Table 7 Overview over outcome onset categorization and exposure definitions used

	Onset	**Primary approach**	**Sensitivity approach**
Primary Outcomes			
GI perforation	Acute	On-treatment	Ever-treated
DILI	Acute	On-treatment	Ever-treated
Bone fracture	Delayed	Ever-treated	On-treatment
Secondary Outcomes			
Malignancy excluding NMSC	Delayed	Ever-treated	
NMSC	Delayed	Ever-treated	
MACE	Acute and delayed	On-treatment	Ever-treated
VTE	Acute	On-treatment	
Serious infections including OI	Acute	On-treatment	
TB	Acute	On-treatment	
HZ	Acute	On-treatment	
All-cause mortality	Delayed	Ever-treated	

9.7.2. Descriptive Analysis

All descriptive statistics will be presented separately for each country. Mean (standard deviation) and median (25th percentile, 75th percentile) will be used as descriptive statistics for continuous variables and counts and proportions for categorical variables.

Descriptive analyses will be conducted to characterize the users and the real-world utilization of upadacitinib and other select biologic IBD treatments to assess suitability of treatment groups as potential comparators to the upadacitinib cohort. These descriptive analyses will provide guidance on potential comparators and feasibility of comparing incidence rates across treatment cohorts.

Drug utilization and patient baseline characteristics (e.g.; demographics, comorbidities and medical history, concomitant treatments, treatment experience, healthcare utilization) will be summarized for upadacitinib and select biologic IBD treatments at each *index date*, separately for each country, by *line of treatment*, IBD diagnosis (UC or CD), dose (upadacitinib), age group, relevant risk factors (e.g., malignancy, VTE, and MACE), and disease history as listed in the secondary objectives (moderate hepatic impairment, HBV & HCV, severe renal impairment).

Separate propensity scores (PS) for each country, *line of treatment,* and IBD diagnosis will be generated for upadacitinib users and users of other select biologic IBD treatments. Logistic regression with treatment cohort as the dependent variable will be used to estimate the PS. Selection of variables to include in the PS modelling will be a factor associated with a reported

increase or decrease in the risk of the safety outcomes of interest (i.e., confounding variables), while excluding covariates only associated with the treatment (i.e., instrumental variables). Prior clinical knowledge and information from previous studies will be used to select an a priori list of potential confounders to be included in the PS model. The distribution/overlap of PS will be examined to assess the balance across cohorts. The standardized mean difference (SMD) will be used to assess comparability across treatment groups if needed.

Descriptive analyses will be performed in the interim report and the final report.

9.7.3. Crude Analyses

Incidence Rates (IRs) will be defined as the number of events divided by the PYs at risk. IRs will be based on the number of cases (n) identified with a safety outcome of interest over the cumulative PYs of follow-up for that outcome and will be displayed as per 1,000 PYs with corresponding exact 95% CIs.

Crude IR estimates for the primary outcome, GI perforation, will be calculated by country, *line of treatment* and IBD diagnosis for the upadacitinib cohort and the comparator cohort.

For the other primary outcomes and secondary outcomes PYs at risk, the number of safety outcomes, and crude incidence rates for upadacitinib will be reported by country, *line of treatment*, IBD diagnosis and relevant risk factors (e.g., malignancy, VTE, and MACE).

If suitable comparator(s) can be identified, crude incidence rates and crude incidence rate ratios for all safety outcomes will be provided for the comparator cohorts as well.

Crude analyses, as applicable, will be performed in the interim report and the final report.

9.7.4. Comparative Analyses

Comparison of rates of GI perforation between upadacitinib and comparators will be made with a Cox regression model, by each *line of treatment* cohorts, using the *on-treatment* exposure definition as time at risk.

If assessed as feasible, based on (1) number of upadacitinib users, (2) number of other select biologic IBD treatments users suitable for comparison, and (3) number of safety events, Cox regression analyses will be performed to compare rates of DILI, bone fracture and all the secondary outcomes between upadacitinib and comparator treatments. Cox regression models will be performed separately for each outcome, stratified by *line of treatment*. Table 7 above specifies the exposure definitions that will be used as time at risk for each outcome.

For malignancy, exposure person-time and time to event will start to be counted from the lag-time of 12 months after *index date*. The hazard ratio (HR) and 95% CI will be reported from the Cox models. Kaplan-Meier curves for all outcomes will also be reported.

For the comparative analyses in Sweden, the study population will be restricted to only patients included in [redacted].

Comparative analyses of GI perforation will be performed in the interim report if number of

patients is sufficient. Comparative analyses on GI perforation and all other outcomes will be performed in the final report, as applicable.

Adjustment for Baseline Imbalances

To adjust for potential confounding at baseline, the outcome models will be weighted with stabilized weights based on the inverse probability of treatment initiation (i.e., propensity score) at baseline. The weights will be constructed to estimate the average treatment effect for the treated. To avoid for potential extreme weights, propensity score will be truncated at the 1% and 99% centile.

Pooling of the Line of Treatment–specific Results

The primary adjusted analysis will pool the results of each *line of treatment* analysis unless evidence exists for a heterogeneity of the effect of upadacitinib on the outcomes of interest across lines of treatment. The homogeneity of the estimates across *line of treatment* strata will be evaluated, separately for each safety outcome, using the I^2 statistic. If the number of outcomes is too small for stable estimations of the heterogeneity, alternative approaches will be considered. Meta-analyses combining results from all three countries will also be performed.

9.7.4.1. Sensitivity Analyses

The following sensitivity analyses will be performed, following the statistical methods described in the previous section.

- Analyses with 0- and 6-months lag time for malignancy outcomes will be conducted
- If number of patients allow, analysis will be conducted among patients with and without prior history of the study outcome being analysed
- For the primary outcomes GI perforation and DILI, analyses will be repeated using the *ever-treated* approach
- For the primary outcome bone fracture, analysis will be repeated using the *on-treatment* approach
- For MACE, analysis will be repeated using the *ever-treated* approach since it can be regarded both as acute onset and delayed onset outcome

9.7.5. Missing data

In Sweden and Denmark using [redacted] as source of data, results in negligible missing values and the very few missing values are not often missing at random (i.e. education level of immigrants). Therefore, missing data will not be imputed but treated as missing. Within each data source, if information on a particular variable is available, patients will be assumed not to have the factor if there is no evidence for its presence (i.e., values for variables used in a given data source will not be considered missing). The only exception to this principle will be in the situation where "missing" is one of the possible values recorded for the variable, in which case the value as listed within the data source will be retained in the analysis as one of the possible values (e.g., a

variable can be "yes" "no" or "missing").

9.8. Quality Control

Several variables in the original data are subject to logical checks at the time of data entry. Several range checks exist for variables that are represented as integers; acceptable values depend on the clinical context. During the preparation of the analytic file for this study, quality-control measures will include checks for legitimate values for each categorical variable and logic checks for dates. There are no plans to systematically clean the original data via queries after data are received.

The chart abstraction data in Spain will be checked for content by edit checks programmed into the electronic questionnaire, as stated in the edit check specifications document that will be prepared. In addition, sites will be queried for nonsensical data (e.g., dates that are in the wrong format).

Data storage, management and analyses will be conducted according to the standard operating procedures of each research partner. At a minimum, the SAP and the statistical programming and analyses will be reviewed and supervised by a senior statistician and all study documents (protocol, report, and publications) will be reviewed by the entire research team. A senior epidemiologist from each research partners supervise the project and will review the output before submission to the MAH. Clinical expertise is available for appropriate interpretation of results. All project staff members receive comprehensive orientation training and are regularly trained.

At the start of the project, a regular communication plan will be established (via e-mail and regular teleconferences), and internal timelines will be established to allow review and quality control before submitting each deliverable. Each research partner will also follow its internal quality control procedures and will ensure the necessary compliance with local data protection, storage and archiving, patient privacy laws and regulations, and will obtain all permission necessary to conduct this study.

All analyses will be conducted according to the Guidelines for Good Pharmacoepidemiology Practices [102], the Guideline Good pharmacovigilance practices [103] and The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [104].

9.9. Limitations of the Research Methods

This non-interventional registry-based PASS aims to evaluate the long-term safety of upadacitinib in the treatment of patients with moderate-to-severe active UC and CD using data collected based on routine clinical practice. Specific areas that can be potential limitations have been considered in the study design and planned analysis.

Some detailed clinical information is not collected in the [redacted] including score-based IBD disease severity and patient reported outcomes. Information on IBD diagnosis is retrieved from the [redacted] covering only patients treated in specialist care. Since IBD is predominantly

managed by gastroenterology specialists rather than primary care physicians in the study countries, and the use of the IBD quality registries in this study, misclassification of these patients using these data sources is unlikely [105].

Event misclassification due to the real-world nature of the data, as opposed to a randomized clinical trial. As with other studies using data collected from routine clinical practice, the level of ascertainment of study events may not be optimal. Specific algorithms for detecting the outcome variables [redacted] have not been validated, [redacted] have been validated several times [106]. The overall PPV of the inpatient diagnoses generally ranged from 85% to 95%. Some outcomes like NMSC may also be affected by detection bias. In Spain, outcomes will be verified using medical record review (i.e., all outcomes occurring among upadacitinib initiators and a random sample of events from the comparator initiators cohort).

For the comparator treatments, exposure to biologics in Sweden will not have complete coverage in the [redacted] in those instances when it is given in clinics intravenously and the patient has not filled a pharmacy prescription. Therefore, [redacted] will also be used in Sweden to capture exposure information and the comparative analyses between treatment cohorts will be restricted to patients included in [redacted].

Channeling "more severe" patients onto a new medication is a common phenomenon in pharmacoepidemiology. Patients starting treatment with a newly marketed drug might have more severe disease than patients not taking the medication. Patients may also have a less severe form of the disease if physicians prefer to test new drugs with a less familiar safety profile in less severely affected patients. The observed risk may change over time as the users of upadacitinib expands into less selected patients or specific subgroups. The potential for channeling bias for upadacitinib will be minimized by selecting biologic treatments in the comparator cohort that are at the same *line of treatment* as upadacitinib for the treatment of IBD and by characterizing patients at the *index date*.

Residual confounding due to lack of complete information on potential confounders. The validity of proxies to identify some potential confounders like smoking or alcohol use may be limited. Relevant confounders like disease activity/severity will be addressed using proxies, and also the main analysis will be stratified by number of previous biologic treatments in order to improve comparability between cohorts. Confounders will be identified and adjusted for and the potential for residual confounding will be considered. In Spain, to maximize the capture of relevant variables, the study will rely on data collected in [redacted] for all study patients (as available) and information abstracted from the patients' medical records for all upadacitinib initiators and for all the biologic treatment initiators who are randomly selected for participation in the study. Propensity scores may be developed for adjustment purposes and will be based on confounders as available. Potential lack of information on covariates is expected to be non-differential in nature. The role of unmeasured confounding and its influence on the study results will be discussed in the reports.

Potential limited study size: As in all safety studies, the relevant parameters to consider for the interpretation of the results focus on the point estimate and the upper limit of the CI. The number

of upadacitinib users may be low, which would result in limited precision of the risk estimates for the study outcomes. Additionally, the number of main outcomes is also expected to be low, and therefore may contribute to the potential imprecision of estimates.

The results of this study will likely reflect country-specific healthcare practices for the treatment of patients with IBD in Denmark, Sweden, and Spain, which may not be fully applicable to other countries. However, under the umbrella of the centralized European system of drug approval, we expect that the results of the study should be generally applicable to most European countries that have a public healthcare system with universal coverage.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

Differences in legislation may exist across the three countries. The research in each country participating is governed by rules that guarantee the integrity of data and the privacy of individuals.

In Denmark, the study is based on register data only and will not require informed consent. No Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval is required for studies based on data from routine registries. An approval from the Danish Data Protection Agency, required for all studies, will be obtained, and the study will be registered with Aarhus University, as required.

In Sweden, the study is based on register data only and will not require informed consent. An IEC approval will be obtained from the Swedish Ethical Review Authority. Approval from the Swedish Data Protection Agency is not required. The register holders will review the data requests, and after approval the linked individual-level data will be pseudonymized by replacing the PIN with a project specific unique number. Country-specific data will be kept in secure servers at Statistics Denmark and at Karolinska Institutet, and only members of the investigator teams will have access to the data in their respective countries.

In Spain, the study protocol will be reviewed and endorsed by [redacted] and the study's reference ethics committee (to be determined). In addition, the ethics committee of each hospital participating in the study's chart review component will also review and approve the protocol, commensurate with local law. In addition, RTI-HS will obtain approval or exemption from the RTI International IRB.

Patients whose data are included in the [redacted] have previously consented to have their health information included in this database. For the current study, some of the variables of interest (e.g., VTE risk factors, hyperlipidaemia) extend beyond the field of IBD and are not routinely collected in [redacted] data. Consequently, a new informed consent form will need to be obtained for this PASS for all patients who participate in the chart abstraction component of the study. Patients who do not sign the informed consent may be part of the study for the

outcomes that are correctly captured in the [redacted].

Physician sites participating in medical record abstraction will be paid nominal incentives to compensate them for the time spent providing data from patient records, per country-specific regulations. The amount and payment methods will be reviewed and approved by the ethics committee to ensure that payments are commensurate with the time needed to complete the study tasks and are not coercive.

The investigators will comply with the EU General Data Protection Regulation (GDPR) and its implementation in the national legislations by May 2018 in the processing of personal data. Additionally, investigators will adhere to commonly accepted research practices, including those described in the following guidance documents: ENCePP Guide on Methodological Standards in Pharmacoepidemiology, ENCePP Code of conduct, Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

All data collected in the study will be de-identified with no breach of confidentiality regarding personal identifiers or health information. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing study participants' data. The research team will not have access to any participant-identifying information. Only de-identified data will be made available to the research staff and AbbVie. Thus, any reports generated will not contain any participant identifiers. Data will be provided to AbbVie in aggregate form only and will not be linked to patients or healthcare providers.

11. Management and Reporting of Adverse Events/Adverse Reactions

Causality assessment at the individual case level is not feasible in a study using large health care registers or electronic health care records. This is a non-interventional study based on data already collected under routine clinical care; therefore, adverse events reporting at the individual case level will not be required. See also Good pharmacovigilance practices (GVP), Module VI Section VI.C.1.2.1.2 for guidance on reporting of adverse events in Non-interventional post-authorization studies with a design based on secondary use of data. Any risk identified from the analyses, not already reported as outcomes of the study (or part of a sensitivity analysis), will be summarized in section 10.6 of the study reports. See also EMA guidance for the format and content of the final study report of non-interventional post-authorization safety studies Section 10.6 Adverse events/adverse reactions.

12. Plans for Disseminating and Communicating Study Results

The independent investigators will prepare annual progress reports, an interim report and a final study report. AbbVie will review the reports before submission to the authorities.

The study will be registered on ENCePP European Union electronic Register of Post-Authorization Studies (EU PAS Register) (http://www.encepp.eu/encepp_studies/indexRegister.shtml), within 30 calendar days after the study protocol is finalized and approved by the regulatory agency. The

study protocol will be disclosed to the EU PAS Register within a target of 14 calendar days following the end of data collection. The study findings will be disclosed within 30 business days after the study report is finalized and shared with the regulatory agency.

The investigators may present results included in reports of this study at scientific conferences and in peer-reviewed journals, after completion of the study. The investigators have the right to publish the results independently of the sponsor. Publications will follow guidelines, including those for authorship, established by the International Committee of Medical Journal Editors [107]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Checklist will be followed.

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14. Annex 1. List of Stand-Alone Documents

None.

15. Annex 2. ENCePP Checklist for Study Protocols

Study title: Cohort Study of Long-term Safety of Upadacitinib for the Treatment of Ulcerative Colitis and Crohn's Disease in a Real-world Setting in Europe

EU PAS Register® number: will be registered following regulatory endorsement and prior to start of data collection
Study reference number (if applicable): N/A

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)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
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)	☒	☐	☐	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?	☐	☐	☒	

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

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	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))	☒	☐	☐	9.7
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	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.1
	4.2.4 Disease/indication	☒	☐	☐	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

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)	☒	☐	☐	9.3
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?	☒	☐	☐	9.3

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3
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?	☒	☐	☐	9.1

Comments:

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, 9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, Annex 3
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:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3, 9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7, 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3

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)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

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

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

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)	☒	☐	☐	9.6,9.8,10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

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
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

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: 04 July 2023

Signature: _____

Signature page

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16. Annex 3. Additional Information

The tables with the variables below are not definite. Codes and definitions will be refined and further specified before data extraction in the SAP.

Table 8 Disease codes to be used in [redacted]

ICD-10 Codes	Register	Description
Ulcerative Colitis		
[redacted]	Patient	
Crohn's disease		
[redacted]		
Moderate hepatic impairment		
[redacted]	Patient	Sub-population for secondary objectives
Chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV)		
[redacted]		Sub-population for secondary objectives
Severe renal impairment		
[redacted]	Patient	Sub-population for secondary objectives Country specific procedure codes for Dialysis may be added

Table 9 Treatment codes to be used in [redacted]

Substance	ATC code	[redacted]	Defined Daily Dose
Upadacitinib	[redacted]		15 mg (oral)
Biologic comparator treatments (other biologic treatments approved for moderate-severe UC during the study period might be included)			
Adalimumab	[redacted]	[redacted]	2.9 mg (parenteral)
Golimumab			1.66 mg (parenteral)
Infliximab			3.75 mg (parenteral)
Vedolizumab			5.4 mg (parenteral)
Ustekinumab			0.54 mg (parenteral)
Risankizumab			1.67 mg (parenteral)

Table 10 Outcomes in [redacted]

Diagnosis Codes (ATC and ICD-10)	*Register*	*History exclusion look-back period*	*Description*
Gastrointestinal (GI) perforations			
[redacted]	Patient		
Bone fracture [108]			
[redacted]	Patient		Any fracture
Drug-induced liver injury (DILI)			
[redacted]	Patient		Toxic liver disease
Malignancies excluding NMSC			
[redacted]	Cancer/Patient	5 years	
Non-melanoma skin cancer (NMSC)			
[redacted]	Cancer/Patient	5 years	
MACE (non-fatal MI, non-fatal stroke, cardiovascular death)			
[redacted]	Patient, Cause of Death		
Venous thromboembolic events (VTE)			
[redacted]	Patient		
Serious infections (any hospital-treated infections, including opportunistic infections)			
[redacted]	Patient		Respiratory tract infections. In-patient only
[redacted]	Patient		Infections of the gastrointestinal tract In-patient only
[redacted]	Patient		Urinary tract infection In-patient only
[redacted]	Patient		Infections of the skin and subcutaneous tissue In-patient only

[redacted]	Patient		Other infections In-patient only
Herpes zoster (HZ)			
[redacted]	Patient		
Active tuberculosis (TB)			
[redacted]	[redacted]		[redacted]
All-cause mortality			
[redacted]	[redacted]		[redacted]

Table 11 Safety Study Outcomes, Operationalisation in [redacted] and Outcome-specific Risk Windows

Outcome	Description	Operationalisation
Primary outcomes		
Serious and opportunistic infections (including active TB)	Record of a first serious or opportunistic infection requiring hospitalisation, within the risk window	[redacted]
Herpes zoster	Record of a first Herpes zoster requiring and not requiring hospitalisation, within the risk window	
Malignancies (excluding NMSC)	Record of a first ever primary invasive malignancy of any type within the risk window	
NMSC	Record of a first NMSC within the risk window	
MACE	Record of a first non-fatal acute myocardial infarction, non-fatal stroke within the risk window Record of cardiovascular death within the risk window	
VTEs (including DVTs and PE)	Record of a first VTE or PE requiring hospitalisation within the risk window	
Secondary outcomes		
GI perforation	Record of a first GI perforation requiring hospitalisation within the risk window	[redacted]
DILI	Record of a first DILI within the risk window	
Bone fractures	Record of a first bone fracture within the risk window	
All-cause mortality	Record of death of any cause within the risk window	

Table 12 Covariates in [redacted] in Spain

Data type	Automated [redacted] Data	[redacted]
Patient identifiers	Patient identification number Site identifier	Not required
Exposure	Treatment information (upadacitinib and biologic treatment comparators) – Date of treatment initiation – Initial dose – Days of drug supplied – Dates of dose changes – Date of discontinuation	Not required
Demographics	Year of birth Sex	Not required
Lifestyle factors	some captured through specific fields (familial history of specific conditions, smoking habit and comorbidities, but likely underrecorded)	Yes, available from patients' [redacted] (questionnaire)
Comorbidities	Through specific fields for some comorbidities (hypertension, diabetes, heart disease, chronic kidney disease, rheumatoid arthritis, cirrhosis, stroke, dyslipidaemia); however, likely underrecorded. Some risk factors for study outcomes captured through specific fields (family history of specific conditions, smoking habit and comorbidities) however, likely underrecorded. Renal impairment, i.e., severe renal impairment through diagnosis. No laboratory test data or results.	Yes, available from patients' [redacted] (questionnaire)
IBD Common extraintestinal manifestations [67]		Yes, available from patients' [redacted] (questionnaire)
IBD Treatment History	Yes	Not required

Data type	[redacted]	[redacted]
Extent and localization of IBD [68]	IBD clinical information – Date of first diagnosis of IBD – Disease duration – Extend of disease – Disease location (proctitis / left-sided colitis / pancolitis) – Presence of stoma Diagnostic and surgical procedures – Endoscopies/colonoscopies, dates and results only if performed for colorectal screening – Colectomies	IBD clinical information – Specific disease location and dates – Presence of Stoma Diagnostic and surgical procedures – Endoscopies/colonoscopies, dates and results – Colectomies
IBD severity (Spain only)	IBD severity* – Date of severity assessment – PMS and components (UC only) – HBI and components (CD only) – Stools/day – Blood in stools – Nocturnal stools – Other severity variables faecal calprotectin, C-reactive protein, haemoglobin (not in all patients but in a great proportion, at least once per year) *Note: IBD activity data are updated/overwritten at each clinical visit	IBD severity – Date of severity assessment – partial Mayo score and components (UC only) – HBI and components (CD only) – Stools/day – Blood in stools – Nocturnal stools – Other severity variables
Laboratory test and results		Yes, available from patients' [redacted] (questionnaire)
Medication use within 1 year prior to *index date*	No	Yes, available from patients' [redacted] (questionnaire)
Previous history of outcomes	See Table 11	See Table 11
VTE risk factors [69]	See Comorbidities	Yes, available from patients' [redacted] (questionnaire)
Subgroups of interest	Very elderly (aged ≥ 75 years) Untreated chronic hepatitis B or C Moderate hepatic impairment captured through diagnosis	Not required