Study Protocol

Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe

Marketing Authorisation Holder: AbbVie Deutschland GmbH & Co. KG (EU), AbbVie Inc (US)
Study number: P24-344

PASS Information

Title	Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe
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Marketing authorisation holder(s)	EU: AbbVie Deutschland GmbH & Co. KG US: AbbVie Inc.
Joint PASS	No
Research question and objectives	The study aims to evaluate the use of upadacitinib in patients with ulcerative colitis (UC) in routine clinical care in Denmark, Sweden, and Spain. The study objectives are: 1. To describe the baseline characteristics of patients with UC who are new users of upadacitinib. 2. To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the additional risk minimisation measures (aRMMs) among patients with UC who are new users of upadacitinib, by: a. Quantifying the compliance to recommendations for posology (average daily dose) and duration of use; b. Quantifying the compliance to recommendations for the use among patients who have risk factors for gastrointestinal (GI) perforation, malignancy, major adverse cardiovascular events (MACE), venous thromboembolic events (VTE), and serious infections; c. Quantifying the compliance to the recommendations for the use among patients aged 65 years and older; d. Quantifying the compliance to the recommendations for contraindicated use including pregnancy and active tuberculosis (TB); e. Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only).

	3. To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically: a. Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b. Describe the use of upadacitinib among patients aged 65 years and older; c. Describe the use of higher maintenance dose of upadacitinib 30 mg.
Country(-ies) of study	Denmark, Spain, Sweden
Authors	[redacted]

Marketing authorisation holder(s)

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Project Title: Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe

Principal Investigator:	[redacted], on behalf of the entire study research team
Version:	1.2
Version Date:	10 November 2023

[redacted] _____ [redacted]

Date

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2. List of abbreviations

Abbreviation	Descriptions
aRMMs	Additional Risk Minimisation Measures
ATC	Anatomical Therapeutic Chemical classification
BioIBD	Danish Database for BIOlogical treatment of Inflammatory Bowel Diseases
CPE	Centre for Pharmacoepidemiology
[redacted]	[redacted]
DMSc	Doctor of Medical Science
DSc	Doctor of Science
DVT	Deep venous thrombosis
eCRF	Electronic case report form
EMR	Electronic medical record
[redacted]	[redacted]
GI	Gastrointestinal
EMA	European Medicines Agency
EU	European Union
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GDPR	General Data Protection Regulation
GETECCU	Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
HDL	High-density lipoprotein
HZ	Herpes Zoster
IBD	Inflammatory bowel disease
ICD-10	International Classification of Diseases, Tenth Edition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JAK	Janus kinase
LDL	Low-density lipoprotein
LMP	Last menstrual period
MACE	Major Adverse Cardiovascular Events
MAH	Marketing authorization holder
MSc	Master of Science
MD	Medical Doctor
MPH	Master of Public Health

NA	Not available
[redacted]	[redacted]
NSAID	Nonsteroidal anti-inflammatory drug
PAS	Post-authorisation studies
PASS	Post-authorisation safety studies
[redacted]	[redacted]
RTI-HS	RTI Health Solutions
PE	Pulmonary embolism
PhD	Doctor of Philosophy
PIN	Personal identity number
SAP	Statistical analysis plan
ScD	Doctor of Science
[redacted]	[redacted]
SID	Study identification number
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
[redacted]	[redacted]
TB	Tuberculosis
TYK	Tyrosine Kinase
UC	Ulcerative Colitis
US	United States
VTE	Venous Thromboembolic Events
WHO	World Health Organization

3. Responsible parties

Parties	Name, Degree(s)	Title/Role	Affiliation	Address
Principal investigator	[redacted]	[redacted]	Centre for Pharmaco-epidemiology, Karolinska Institutet	[redacted]
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Coordinating investigators, Spain	[redacted]		RTI Health Solutions	
	[redacted]		RTI Health Solutions	
Co-investigators, [redacted]	[redacted]		Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) [redacted]	
	[redacted]		GETECCU [redacted]	
Coordinating investigator, Marketing Authorization Holder (MAH)	[redacted]		AbbVie, Inc.	Pharmacovigilance and Patient Safety 1 North Waukegan Road, North Chicago, IL 60064, USA
	[redacted]		AbbVie, Inc.	Pharmacovigilance and Patient Safety 1 North Waukegan Road, North Chicago, IL 60064, USA

4. Abstract

Title:

Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe.

Version 1.2, 10 November 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) is a chronic, relapsing inflammatory disease of the large intestine characterized by diffuse and continuous inflammation and ulceration of mainly the innermost lining of the colon starting from the rectum. UC causes significant physical and psychological burden, as well as significant economic impact. Upadacitinib is an oral selective and reversible inhibitor of Janus Kinase (JAK) which is being developed for the treatment of moderate to severe UC in adults, who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

The recommended induction dose of upadacitinib is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, upadacitinib 45 mg once daily may be continued for an additional 8 weeks. Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. The recommended maintenance dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. A dose of 15 mg is recommended for patients 65 years of age and older and for patients at higher risk of venous thromboembolic events (VTE), major cardiovascular events (MACE) and malignancy. A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment who are not at higher risk of VTE, MACE and malignancy or who do not show adequate therapeutic benefit to 15 mg once daily. The lowest effective dose to maintain response should be used. 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.

As with other JAK inhibitors also marketed in Europe, important safety risks have been identified with upadacitinib that require additional risk minimisation measures (aRMMs) such as a Healthcare Professional (HCP) educational guide and a patient card as detailed in the European Union risk management plan for Rinvoq®, and summary of product characteristics (SmPC). Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 23 January 2023), upadacitinib recommended use and doses have been changed. In addition, gastrointestinal (GI) perforation was identified as an adverse

drug reaction in the upadacitinib extension indication variation procedure for Crohn's disease (CHMP opinion 23 February 2023). The HCP guide has been updated accordingly after these procedures and is focused on the targeted risks: malignancy, MACE, VTE, GI perforation, serious and opportunistic infections including tuberculosis (TB) and herpes zoster (HZ), and fetal malformation following exposure in utero (pregnancy risk).

Using data derived from European registries, this drug utilization study will describe baseline characteristics of patients with UC exposed to upadacitinib and evaluate the aRMMs by providing insights regarding how clinical practice patterns correspond to the listed recommendations in the HCP guide or SmPC when using upadacitinib (Rinvoq®) for UC in routine clinical care.

Research question and objectives:

The study aims to evaluate the use of upadacitinib in patients with UC in routine clinical care in Denmark, Sweden, and Spain.

The study objectives are:

1. To describe the baseline characteristics of patients with UC who are new users of upadacitinib.
2. To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by:
    a. Quantifying the compliance to recommendations for posology (average daily dose) and duration of use;
    b. Quantifying the compliance to recommendations for the use among patients who have risk factors for GI perforation, malignancy, MACE, VTE, and serious infections;
    c. Quantifying the compliance to the recommendations for the use among patients aged 65 years and older;
    d. Quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB;
    e. Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only).
3. To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically:
    a. Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections;

b. Describe the use of upadacitinib among patients aged 65 years and older;

c. Describe the use of higher maintenance dose of upadacitinib 30 mg.

Study design:

The study is a multi-country non-interventional descriptive drug utilization study among new users of upadacitinib (Rinvoq®) for the treatment of UC. Study cohorts will be identified in electronic health care data from Denmark, Sweden, and Spain. In Denmark and Sweden, data will be collected from the [redacted] In Spain, data will be collected from the [redacted] The *study period* ranges from the country-specific date of distribution of aRMM for the treatment of UC in Denmark, Sweden, and Spain until 31 December 2025.

Population:

The study population consists of all patients older than 18 years, with at least [redacted] diagnosis of UC [redacted] and exposure to upadacitinib [redacted] Each patient will be followed from the initiation of upadacitinib to the earliest occurrence of: upadacitinib discontinuation, end of the *study period*, study withdrawal (emigration, withdrawn [redacted], or loss to follow-up), or death.

Variables:

The exposure of interest will be the use of upadacitinib identified through the [redacted] and the [redacted] in Denmark, [redacted] in Sweden, and the [redacted] in Spain.

To describe the baseline characteristics of new users of upadacitinib, the study will include the following baseline variables: demographics, socioeconomic factors, UC disease characteristics, lifestyle risk factors, medical history, and concomitant medications.

To evaluate the aRMMs, the study will include outcome variables related to: malignancy, MACE, GI perforation, VTE, serious and opportunistic infections, contraindicated use, and posology and duration of use.

Data sources:

Data sources for this study in Sweden will be [redacted]

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

Study size:

All eligible initiators of upadacitinib during the study period, in the UC population, will be included.

Data Analysis:

This will be a descriptive study. Upon upadacitinib initiation, baseline characteristics of patients will be assessed. Proportions of outcome variables will be assessed prior to upadacitinib initiation, at upadacitinib initiation and during follow-up, depending on the outcome indicator being reported. The proportion of outcome variables will be calculated as the number of patients for each specific outcome variable over the total number of patients considered for that specific outcome. Utilization of upadacitinib in Sweden will be stratified by the time period before and after the implementation of the revised aRMMs from the Article 20 referral procedure.

Milestones:

Study progress will be reported every year from 2024 to 2026. The final study report will be submitted to the EMA in Q3 2027.

5. Amendments and updates

This protocol version 1.2, dated 10 November 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 1.1, dated 05 September 2023.

This protocol version 1.1, dated 05 September 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 1.0, dated 14 March 2023.

This study (protocol number: P24-344), version 1.0, dated 14 March 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol P23-479, version 1.0, dated 03 October 2022, and will replace P23-479 in the risk management plan for upadacitinib.

6. Milestones

Milestones	Planned Dates
Registration in the EU PASS Register	30 days post protocol approval
Start of data collection for secondary data use (date when data extraction starts in Sweden)[1]	Q1 2024
Study progress report 1[2]	Q3 2024
Study progress report 2	Q3 2025
Study progress report 3	Q3 2026
End of data collection for secondary data use (date when analytical data set is available in all three countries)	Q1 2027
Final report of study results (incl. data up to 31 December 2025)	Q3 2027

[1] Start of data extraction will be different in the three countries due to later price and reimbursement approval for upadacitinib in Denmark and Spain (estimated end of 2023).
[2] Will only include data from Sweden, see footnote [1] above

7. Rationale and background

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the large intestine characterized by diffuse and continuous inflammation and ulceration of mainly the innermost lining of the colon starting from the rectum. Disease activity is characterized by periods of active inflammation alternated with periods of remission [1]. Prevalence of UC varies by age group and onset peaks between the ages of 15 and 30 years. In Sweden, the prevalence of UC is 510 per 100,000 persons [2].

In Spain, the overall incidence of UC ranges from 0.6 to 8.0 per 100,000 persons [3, 4]. Incidence rates vary by geographic regions; in Northern Spain, UC incidence ranges from 12.5 to 13.6 per 100,000 persons [5], in Southern Spain is 7.6 per 100,000 persons, and in Catalonia ranges from 15.4 to 26.5 per 100,000 persons [5].

Clinical manifestations of UC usually include diarrhea commonly with blood, abdominal pain, urgency, tenesmus and incontinence [6]. Additionally, patients living with UC can develop

systemic symptoms that depends on the severity of the intestinal disease, like fever, weight loss and anemia. UC may also present extraintestinal manifestations including arthropathy, uveitis, erythema nodosum, primary sclerosing cholangitis, venous and arterial thromboembolism among others [7, 8]. The severity of the disease may range between mild and severe according to symptoms that are usually assessed using disease activity indexes that take into consideration extraintestinal manifestations, laboratory abnormalities and endoscopic assessment [9]. The majority of patients with UC have a mild to moderate course, but about 10% to 15% of patients experiences an aggressive course with moderate to severe active disease [10, 11]. Moderate to severe UC is a debilitating gastrointestinal (GI) condition with a significant physical, psychological, and economic burden [12, 13].

Without appropriate treatment, UC can result in severe clinical symptoms requiring physician visits, hospitalizations [14], surgeries [15, 16], all negatively affecting quality of life. Categories of treatment options for UC include 1. Systemic and/or locally acting 5ASA; 2. Immunomodulators (e.g., thiopurines or methotrexate); and 3. Targeted therapies (e.g., biologics or novel small molecules such as Janus kinase [JAK] inhibitors) [17, 18]. UC treatment is based on the extent and severity of disease activity. Its aim is to prevent long-term sequelae, using induction and maintenance pharmacologic approaches [10, 19, 20]. Patients with active UC require induction treatment and patients in remission require maintenance treatments. Induction treatment goals for patients with active UC are to achieve remission, represented by mucosal healing and symptomatic control [19]. After clinical remission, the maintenance treatment goal is to prevent clinical and endoscopic relapse with appropriate treatment for long term use [18].

Among available treatments for UC as of May 2023, selection of induction therapy depends on different factors, including patient preferences and characteristics, risk of adverse events, additional medications, patient history, availability of infusion centers, patient adherence and costs. Induction regimens usually include biologic treatments alone or in combination with immunomodulators. Biologic treatments include anti-tumor necrosis factor agents (infliximab, adalimumab, golimumab); or anti-integrin antibody (vedolizumab); or anti-interleukin 12/23 antibody (ustekinumab). The small molecules group includes JAK inhibitor like tofacitinib. Maintenance treatment selection depends also on the treatment used to achieve remission and the response [19].

The JAKs are part of the intracellular response mechanism to interleukins, interferons, and hormones such as erythropoietin, thrombopoietin, and growth hormone. Activation of JAK signaling system is associated with inflammatory diseases and malignancies [21]. Inhibitors of JAK are a family of small molecules classified as immunomodulators that block JAK protein family members, including JAK1, JAK2, JAK3, and Tyrosine kinase 2 (TYK2) [21, 22]. Upadacitinib is an oral selective and reversible JAK1 inhibitor which is being developed for the treatment of moderate to severe UC in adults, who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

The recommended induction dose of upadacitinib is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, upadacitinib 45 mg once daily may

be continued for an additional 8 weeks. Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. The recommended maintenance dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. A dose of 15 mg is recommended for patients 65 years of age and older and for patients at higher risk of venous thromboembolic events (VTE), major cardiovascular events (MACE) and malignancy. A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment who are not at higher risk of VTE, MACE and malignancy or who do not show adequate therapeutic benefit to 15 mg once daily. The lowest effective dose to maintain response should be used. 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.

As with other JAK inhibitors also marketed in Europe (tofacitinib, baricitinib, filgotinib), important safety risks have been identified with upadacitinib that require additional risk minimisation measures (aRMMs) such as a Healthcare Professional (HCP) educational guide and a patient card as detailed in the European Union (EU) risk management plan for upadacitinib (Rinvoq®), and summary of product characteristics (SmPC). The aRMM program for upadacitinib is across indications.

Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 23 January 2023), upadacitinib recommended use and doses have been changed. In addition, GI perforation was identified as an adverse drug reaction in the upadacitinib extension indication variation procedure for Crohn's disease (CHMP opinion 23 February 2023). The HCP guide has been updated accordingly after these procedures and is focused on the targeted risks: malignancy, MACE, VTE, GI perforation, serious and opportunistic infections including tuberculosis (TB) and herpes zoster (HZ), and fetal malformation following exposure in utero (pregnancy risk).

This drug utilization study will evaluate the aRMMs by providing insights regarding how the listed recommendations correspond to clinical practice patterns when using upadacitinib for UC in routine clinical care as well as describing baseline characteristics of patients with UC exposed to upadacitinib.

8. Research question and objectives

The study aims to evaluate the use of upadacitinib in patients with UC in routine clinical care in Denmark, Sweden, and Spain using the [redacted], including the [redacted] selected Danish laboratory monitoring, the [redacted]

The study objectives are:

1. To describe the baseline characteristics of patients with UC who are new users of upadacitinib.
2. To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by:
    a. Quantifying the compliance to recommendations for posology (average daily dose) and duration of use;
    b. Quantifying the compliance to recommendations for the use among patients who have risk factors for GI perforation, malignancy, MACE, VTE, and serious infections;
    c. Quantifying the compliance to the recommendations for the use among patients aged 65 years and older;
    d. Quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB;
    e. Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only).
3. To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically:
    a. Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections;
    b. Describe the use of upadacitinib among patients aged 65 years and older;
    c. Describe the use of higher maintenance dose of upadacitinib 30 mg.

9. Research method

9.1. Study Design

The study is a drug utilization, descriptive, non-interventional cohort study of new users of upadacitinib for the treatment of UC identified in electronic health care data from three European countries: Denmark, Sweden, and Spain.

In Sweden, data will be collected from the [redacted]. In Denmark, data will be collected from the [redacted]. In Spain, data will be collected from the [redacted].

9.2. Setting

The study will be conducted within [redacted] of IBD patients in Sweden, as

well as the [redacted] in Sweden and Denmark, covering populations of approximately [redacted] people, respectively. In Spain, data will be collected from the [redacted]. Details on the data sources are described in Section 9.4.

9.2.1. Source Population and Study Cohorts

The *source population* will be all adult patients with UC and upadacitinib exposure registered in the [redacted] in Denmark, and [redacted] in Spain.

To be eligible for inclusion into the *study cohort* patients must:

- Initiate upadacitinib during the *study period* (see definition in Section 9.2.2.)
- Have [redacted] diagnoses of UC [redacted] before or on the date of upadacitinib initiation [23]
- Be at least 18 years of age on the date of upadacitinib initiation
- Have at least 12 months continuous residency in the respective country (Denmark or Sweden), or have at least 12 months participation in the [redacted] (Spain) on the date of upadacitinib initiation.

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 in the beginning of the disease [24]. Therefore, to reduce misclassification, patients with UC will be identified with at least two diagnoses of UC [redacted]. Two or more diagnoses of UC in the [redacted] has a positive predictive value (PPV) of 79% for UC [23, 25].

9.2.2. Study Period

The *study period* ranges from the country-specific date of distribution of aRMMs for the treatment of UC in Denmark (26 September 2022), Sweden (01 September 2022), and Spain (estimated Q3 2023) until 31 December 2025.

9.2.3. Follow-up

Each patient will be followed from the initiation of upadacitinib to the earliest occurrence of: upadacitinib discontinuation (as described in Section 9.3.1.), end of the *study period*, study withdrawal (emigration in Denmark and Sweden, withdrawn [redacted] or loss to follow-up in Spain) or death.

9.3. Variables

9.3.1. Exposure

Exposure will be based on prescriptions and administrations of upadacitinib. In Sweden, an algorithm to identify exposure using joint information from the [redacted] will be used, which will be defined in the statistical analysis plan (SAP) [26, 27]. In Denmark, exposure will be identified by joining information from the [redacted] and the [redacted] In Spain, exposure will be identified in the [redacted] through pre-defined treatment-specific data fields. 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.

Continuous exposure will be defined based on the first and subsequent prescriptions and administrations, considering the available information in [redacted] (start date & stop date), [redacted] (date of administration), [redacted] (date of dispensation), [redacted] (date of dispensation), [redacted] (date of visit when treatment given), [redacted] (date of procedure), [redacted] (date of initiation & discontinuation date). In the [redacted] each dispensation will be assumed to last for as many days as the total amount of tablets received and upadacitinib discontinuation will be defined once more than 30 days have elapsed after the end of a given dispensation. In [redacted] each administration will be assumed to last for a prespecified number of days (to be defined in the SAP). In [redacted] upadacitinib discontinuation will be defined as the discontinuation/stop date. Patients in the study cohort can only contribute to the study as new users of upadacitinib i.e. only first episode of continuous exposure will be included.

9.3.2. Baseline Characterization Variables

The following variables will be included to describe the baseline characteristics of new users of upadacitinib: (definitions, data sources, codes, and look-back periods specified in Annex 3, Additional information, Table 2 and Table 3):

- Demographic variables e.g., sex, age, region of residence, country of birth
- Body Mass Index as recorded in [redacted]
- Socioeconomic factors e.g., education, employment status, income
- UC disease characteristics
    - Date of confirmed UC diagnosis
    - Extra-intestinal manifestations (Arthritis/arthropathy, uveitis and episcleritis, erythema nodosum and pyoderma gangrenosum, Primary sclerosing cholangitis), identified in [redacted]
    - Active disease, [redacted]
    - Extent and localization of UC (identified through the Montreal Classification in [redacted] and proxies (International Classification of Diseases, Tenth Revision [ICD-10] codes assigned for phenotypes of the Montreal Classification [28]))

- Flares of UC (identified through proxies; *steroid prescriptions, hospitalizations with IBD as main diagnosis, acute IBD surgery, and step up in the treatment ladder)*
- Previous UC treatments in the year prior to upadacitinib initiation
- Number of UC hospitalizations and outpatient visits in the 5 years prior to upadacitinib initiation
- Previous IBD surgeries in the 5 years prior to upadacitinib initiation
- Type of first prescriber of upadacitinib (e.g. gastroenterologist, general practitioner)
- Presence of a stoma (will also be evaluated at *follow-up*)

- Medical history including comorbidities
  - Malignancy
  - Cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, myocardial infarction, and stroke
  - Atherosclerotic disease
  - Diverticular disease
  - Diverticulitis
  - VTE: deep venous thrombosis (DVT) and pulmonary embolism (PE)
  - Inherited coagulation disorder
  - Recent major surgeries
  - Recent serious infection
  - Hepatitis B or C
  - Active TB
  - HZ
  - History of chronic infection
  - Malnutrition
  - Anemia
  - Osteoporosis
  - Chronic kidney disease stage 3+
  - Chronic obstructive pulmonary disease
  - Gastroduodenal ulcer
  - Other immune-mediated inflammatory diseases (e.g. rheumatoid arthritis, atopic dermatitis)
- Lifestyle risk factors
  - History of smoking (identified through proxies in Sweden and Denmark, as recorded in [redacted] in Spain)
  - History of drug or alcohol abuse (identified through proxies in Sweden and Denmark, as recorded in [redacted] in Spain)
- Prior and concomitant medications
  - JAK inhibitors
  - Biologic therapies and biosimilars (e.g., golimumab, vedolizumab, infliximab, adalimumab, ustekinumab)
  - Immunosuppressants (e.g., azathioprine, cyclosporine)
  - Cytochrome P450 (CYP) 3A4 inhibitors (ketoconazole, itraconazole, clarithromycin)

- Systemic corticosteroid
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Opioids
- Combined hormonal contraceptives or hormone replacement therapy

Baseline characteristics will be presented for all patients in the study cohort and for:

- Patients who are 65 years of age or older
- Patients with risk factors for MACE and malignancy
- Patients with severe hepatic impairment (Spain only)
- Patients that are dispensed upadacitinib with a strength of 45 mg (induction dose) for <=8 weeks
- Patients that are dispensed upadacitinib with a strength of 45 mg (induction dose) for >8 weeks
- Patients that are dispensed upadacitinib with a strength of 15 mg for maintenance treatment
- Patients that are dispensed upadacitinib with a strength of 30 mg for maintenance treatment

9.3.3. aRMM Outcome Variables

To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs, the outcome variables described in the following sections will be reported (definition, data sources, codes and look-back periods are given in Annex 3. Additional information, Table 2 and Table 3).

9.3.3.1. Malignancy

According to the HCP guide, upadacitinib should only be used in patients who are considered at risk for malignancy if no suitable treatment alternatives are available. To assess whether this recommendation is being followed, the following outcome variables will be included:

- Proportion of patients who are ≥65 years of age at upadacitinib initiation
- Proportion of patients with current malignancy at upadacitinib initiation or a history of malignancy prior to upadacitinib initiation
- Among patients without a history of malignancy, proportion of patients with a diagnosis of malignancy during *follow-up*
- Among patients with a diagnosis of malignancy during *follow-up*, proportion of patients who continued to receive upadacitinib treatment after the diagnosis
- Proportion of patients who are current smokers or past smokers at upadacitinib initiation (Spain only)

9.3.3.2. MACE

According to the HCP guide, upadacitinib should only be used in patients who are considered at risk for MACE if no suitable treatment alternatives are available. To assess whether this recommendation is being followed, the following outcome variables will be included:

- Proportion of patients who are ≥65 years of age at upadacitinib initiation

- Proportion of patients with a history of atherosclerotic disease prior to upadacitinib initiation
- Proportion of patients with a history of other cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, myocardial infarction, and stroke prior to upadacitinib initiation
- Among patients without a history of other cardiovascular risk factors, proportion of patients with cardiovascular event during *follow-up*
- Among patients with a cardiovascular event during *follow-up*, proportion of patients who continued to receive upadacitinib treatment after the event
- Proportion of patients who are current smokers or past smokers at upadacitinib initiation (Spain only)

Treatment with upadacitinib was associated with dose-dependent increase in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). The HCP guide recommends physicians to evaluate lipid level 12 weeks after starting upadacitinib, as well as monitor and manage lipid levels during treatment. To describe the number of patients being monitored for lipid levels while being treated with upadacitinib, the following outcome variables will be included:

- Proportion of patients treated with lipid lowering drugs during *follow-up*
- Proportion of patients with laboratory tests for LDL-C, HDL-C, and total cholesterol taken anytime during *follow-up* (Denmark and Spain only)
- Among patients with laboratory tests for LDL-C, HDL-C, and total cholesterol taken during *follow-up*, proportion of patients with at least one value out-of-range, as assessed by the laboratory taking the laboratory test (Denmark and Spain only)
- Proportion of patients with laboratory tests for LDL-C, HDL-C, and total cholesterol taken 10-14 weeks (70-98 days) after initiation of upadacitinib (Denmark and Spain only)

9.3.3.3. GI perforation

The HCP guide recommends using upadacitinib with caution in patients who might be at risk for GI perforation and the following outcome variables will be included, to assess the recommendation:

- Proportion of patients with a history of diverticulitis prior to upadacitinib initiation (Denmark and Sweden only)
- Proportion of patients recently treated with NSAIDs, systemic corticosteroids, or opioids prior to upadacitinib initiation (Denmark and Sweden only)
- Proportion of patients with diverticulitis or GI perforation during *follow-up* (Denmark and Sweden only)
- Among patients with diverticulitis or GI perforation during *follow-up*, proportion of patients who continued to receive upadacitinib treatment after diagnosis (Denmark and Sweden only)

9.3.3.4. Venous thromboembolic events

The HCP guide recommends using upadacitinib with caution in patients at high risk of VTE due to risk factors other than MACE or malignancy risk factors. To assess whether the recommendations

are being followed, the following outcome variables will be included:

- Proportion of patients with a history of VTE prior to upadacitinib initiation
- Proportion of patients with a recent major surgery prior to upadacitinib initiation
- Proportion of individuals with use of combined hormonal contraceptives or hormone replacement therapy prior to upadacitinib initiation
- Proportion of individuals with inherited coagulation disorder prior to upadacitinib initiation

Physicians are also recommended to discontinue upadacitinib treatment when a patient experience a VTE. To assess whether this recommendation is being followed the following outcome variables will be included:

- Among patients without a history of VTE, proportion of patients with at least one diagnosis of VTE during *follow-up*
- Among patients with at least one diagnosis of VTE during *follow-up*, proportion of patients treated with upadacitinib within the 6 months following the VTE diagnosis

9.3.3.5. Serious and opportunistic infections

The HCP guide states that upadacitinib increases the risk of serious infections, including opportunistic infections and physicians are recommended not to prescribe upadacitinib to patients with active serious infections. Active serious infection is listed as a contraindication to upadacitinib use in the SmPC (covered in Section 9.3.3.6). Since there is a higher incidence of infections in the elderly and in diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Further, there is an increased risk of herpes zoster. The following outcome variables will be included to assess whether the recommendations are being followed:

- Serious infections
  - Proportion of patients who are ≥65 years of age at upadacitinib initiation
  - Proportion of patients with diabetes at upadacitinib initiation
  - Proportion of patients with recent serious infection at upadacitinib initiation
  - Proportion of patients with a history of a chronic infection prior to upadacitinib initiation
  - Proportion of patients with a dispensed prescription/administration of an anti-viral treatment during *follow-up.*
  - Among patients with a serious infection during *follow-up*, proportion of patients who continued to receive upadacitinib treatment after the diagnosis
- Hepatitis B and C
  - Proportion of patients with a history of hepatitis B or C prior to upadacitinib initiation
  - Among patients without a history of hepatitis B or C, proportion with diagnosis of hepatitis B or C during *follow-up*
- HZ
  - Proportion of patients with active HZ at upadacitinib initiation
  - Proportion of patients with at least one diagnosis of HZ during *follow-up*

In the HCP guide physicians are recommended to screen patients before prescribing upadacitinib.

The following outcome variables will be included to assess whether the recommendations are being followed:

- Proportion of patients with laboratory tests for absolute lymphocyte and absolute neutrophil counts in the 60 days period prior to upadacitinib initiation or during *follow-up* (Denmark and Spain only)
- Among patients with laboratory tests for absolute lymphocyte and absolute neutrophil performed during *follow-up*, proportion of patients with at least one value out-of-range, as assessed by the laboratory taking the laboratory test (Denmark and Spain only)
- Among patients with a low laboratory tests for lymphocytes and absolute neutrophil counts taken during *follow-up*, the number of laboratory tests taken within the following 6 months (Denmark and Spain only)

The HCP guide states that live, attenuated vaccines (e.g., measles/mumps/rubella, influenza nasal spray, oral polio, yellow fever, Zostavax™) should not be administered during, or immediately prior to starting upadacitinib treatment. The outcome variable will be included to assess whether this recommendation is being followed:

- Proportion of patients receiving a live attenuated virus vaccination in the 60 days prior to upadacitinib initiation or during *follow-up* (Denmark and Spain only)

9.3.3.6. Contraindications

Upadacitinib is contraindicated during pregnancy and in patients with, severe hepatic impairment, and active TB in the SmPC. The HCP guide states that women who are able to have children should use effective contraception both during treatment, and for 4 weeks after stopping upadacitinib treatment.

To quantify the above-mentioned contraindicated use of upadacitinib in the aRMMs, the following outcome variables will be included for patients with UC:

- Pregnancy
    - Proportion of women who are pregnant (date of last menstrual period [LMP] to date of delivery) when initiating upadacitinib
    - Proportion of women who become pregnant (date of LMP) during *follow-up*
    - Among women who become pregnant while receiving upadacitinib, proportion of women who continued to receive upadacitinib treatment after becoming pregnant
- Active TB
    - Proportion of patients with a history of active TB prior to upadacitinib initiation
    - Among patients without a history of active TB, proportion diagnosed with active TB during *follow-up*
    - Proportion of patients with laboratory tests for active TB in the 60 days prior to upadacitinib initiation (Denmark and Spain only)

9.3.3.7. Posology and duration of use

The SmPC recommends dosing for patients with UC. To describe upadacitinib use among all patients with UC in the overall study cohort, the following will be described:

- Proportion of patients who are treated with upadacitinib with a strength of 45 mg (induction dose) for 0 days, 1 to 56 days, 57 to 112 days and greater than 112 days, respectively
- Proportion of patients who are treated with upadacitinib with a strength of 15 mg or 30 mg (maintenance doses) respectively

According to the HCP guide, the 30 mg upadacitinib maintenance dose is recommended in patients with high disease burden or in patients who do not benefit from the 15 mg dose, who are not at risk of VTE, MACE or malignancy. 15 mg upadacitinib should be used in patients who are above 65 years of age or are considered at risk for VTE, MACE or malignancy. 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. To describe upadacitinib use among patients with UC in these populations, the following will be described:

- Proportion of patients who are treated with upadacitinib with a strength of 45 mg (induction dose) for 0 days, 1 to 56 days, 57 to 112 days and greater than 112 days, respectively
- Proportion of patients who are treated with upadacitinib with a strength of 15 mg or 30 mg (maintenance doses) respectively

The HCP guide contains recommendations regarding dosing specific to the UC indication in special subpopulations. To describe upadacitinib use among patients with UC in these special populations, the following will be described:

- Patients with severe renal impairment
    - Proportion of patients who are treated with upadacitinib with a strength of 45 mg (induction dose)
    - Proportion of patients who are treated with upadacitinib with a strength of 30 mg (induction dose) for 0 days, 1 to 56 days, 57 to 112 days and greater than 112 days, respectively
    - Proportion of patients who are treated with upadacitinib with a strength of 30 mg in the maintenance phase. Maintenance phase is assumed to start from day 113 after initiation of upadacitinib

- Patients receiving strong inhibitors of CYP3A4 (clarithromycin, itraconazole, ketoconazole)
    - Proportion of patients who are treated with upadacitinib with a strength of 45 mg (induction dose)
    - Proportion of patients who are treated with upadacitinib with a strength of 30 mg (induction dose) for 0 days, 1 to 56 days, 57 to 112 days and greater than 112 days, respectively

- Proportion of patients who are treated with upadacitinib with a strength of 30 mg in the maintenance phase. Maintenance phase is assumed to start from day 113 after initiation of upadacitinib
- Proportion of patients treated with strong CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, ketoconazole) during continuous treatment of upadacitinib with a strength of 15 mg and 30 mg, respectively

Information about physician prescribed dose is not available in any of the study countries. Therefore, strength of the dispensed substance will be used as a proxy for dose. Each patient is assumed to take one tablet per day of the strength that is prescribed. Dispensed prescriptions with a strength of 45 mg of upadacitinib will be used to identify length of induction dose for the full study cohort.

9.4. Data sources

9.4.1. Denmark and Sweden

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

In Denmark, data from the [redacted] will be used, [redacted]

The assignment of unique personal identity numbers (PIN) to all Danish and Swedish residents at birth or upon immigration makes it possible to cross-link data between the [redacted] within each country [32-34]. The PIN is kept unchanged throughout life, so individuals can be followed-up throughout their lifetime, except for migrants. [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] in Sweden and Denmark contain the following information:

- From the [redacted] in Sweden information on demographic variables, migration and socioeconomic factors will be obtained.
- In Denmark demographic variables and migration will be obtained from the Civil Registration System, while socioeconomic factors will be obtained from [redacted]
- The [redacted] contain information on all hospitalizations and outpatient visits to specialist care, including primary and secondary diagnoses recorded at discharge. Diagnoses of UC, medical history, comorbidities, and outcomes are recorded according to the ICD-10.
- The [redacted] contain information on all incident primary cancer diagnoses (morphologically verified). Additional information about cancer diagnoses may be obtained from the NPRs.
- The date and cause of death will be obtained from the [redacted]. In Denmark, the civil registration system will be used for identifying date of death.
- [redacted] include data on the formulations and date of all dispensed prescriptions. Drugs are categorized according to the World Health Organization (WHO) Anatomical Therapeutic Chemical classification system (ATC codes) [35]. Main exposure in Sweden will be defined based on [redacted] while in Denmark exposure will be captured by the [redacted]. When captured by [redacted] information about dose, strength, amount dispensed will not be available.
- [redacted] include data on practically all deliveries in Sweden and Denmark including stillborn after week 22, respectively. It is compulsory for every health care provider to report to the registers and the information available is collected from medical records from the prenatal care, delivery care and neonatal care.
- The [redacted] provides events reported according to the Communicable Diseases Act and the communicable diseases ordinance on diseases (e.g. TB) that have mandatory reporting in Sweden.

[redacted]. 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.

Sweden	Denmark
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]

9.4.2. Spain

The study will use data collected from the [redacted] in Spain. [redacted] and that are determined to have research-quality data. This determination is made based on a predetermined threshold for the percentage of patients within a site who are considered "complete" according to predefined critical variables. To be considered complete, a patient cannot have a missing value for the following variables:

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.

Participating sites enter data into an electronic case report form (eCRF) based on routine clinical practice, [redacted]

The information collected from the [redacted] will be supplemented by the participation of clinical investigators at patient sites in additional [redacted]

The general organisation of data sources, research team, and flow of information for the study is presented in Figure 1.

Figure 1 Organisation and Flow of Study Data for [redacted]

[redacted]

9.5. Study size

Not applicable for a drug utilization study. All initiators of upadacitinib during the study period, in the UC population, will be included in the study. No comparative analyses will be conducted.

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

In Denmark, pseudonymized data (replacing PIN with a unique dummy identification number) from the [redacted] will be provided by Statistics Denmark or the Danish Health Data Authority. The health register data will be accessed on-line via a password protected safe data portal.

In Sweden, pseudonymized data (replacing PIN with a unique dummy study identification number) from the [redacted] will be provided by the Swedish National Board of Health and Welfare. Population data will be provided by Statistics Sweden. The pseudonymized individual-level data will be stored at a secure server at Karolinska Institutet, and only members of the research team will have access to the data.

In Spain, the automated data are maintained and managed by the [redacted] in a password-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 [redacted] 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 [redacted] the details of which will appear in a stand-alone Data Management Procedures manual. This manual will also include procedures for contacting sites for [redacted], 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 sponsor. 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

9.7.1. Descriptive analysis

All analyses will be descriptive; no statistical tests will be performed.

For continuous variables, mean, standard deviation, median, 25th and 75th percentiles, minimum

and maximum values and the number of missing values will be reported, when possible. For categorical variables, the frequency, proportion, and number of missing values will be reported. All analysis details, including calculated variables and the proposed format and content of tables, will be detailed in the statistical analysis plan.

Upon upadacitinib initiation, characteristics of patients as described in Section 9.3.2. will be assessed.

Proportions of the outcome variables will be assessed prior to upadacitinib initiation, at upadacitinib initiation and during *follow-up*, depending on the outcome variable being reported. The proportion of the outcome variables will be calculated as the number of patients for each specific outcome variable over the total number of patients considered for that specific outcome (as described in Section 9.3.3.).

Following the procedure under Article 20 of Regulation (EC) No 726/2004, upadacitinib recommended use and doses changed for selected subgroups, during Q2 2023. Upadacitinib is only recommended if no suitable treatment alternatives are available for individuals 65 years of age or older, or individuals with risk factors for malignancy or MACE. In addition, upadacitinib should only be used with caution in individuals with risk for VTE.

Therefore, the utilization of upadacitinib in Sweden will be stratified by the time period before and after the distribution of the new HCP guide (05 May 2023). Change in proportions of users over time will be explored graphically by plotting proportions for each 4 months during the study period, if it is possible according to observed frequencies.

Descriptive analyses will be performed separately for each country; summary statistics may be combined across countries, when appropriate.

9.7.2. Missing data

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").

Missing data will not be imputed but treated as 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 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 [56], the Guideline Good pharmacovigilance practices (EMA) [57] and The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [58].

9.9. Limitations of the research methods

- There is potential for information bias.
    - The [redacted] may not contain complete information on all relevant study variables. Many fields are not mandatory for sites to complete.
    - Based on discussions with [redacted] investigators, the true frequencies of certain medical events and laboratory test data unrelated to UC (e.g., VTE, lipid panels) are expected to be underestimated. However, the investigators also indicated that capture of the main study outcomes is reasonably complete. [redacted] is planned for all patients to augment capture of information for variables that are not captured or that are not considered complete in the [redacted] data.
- In Spain, the database structure may also limit the ability to address certain study questions. For example, disease extent is not stored as a time-dependent variable; rather, it is continually updated and at any point reflects the maximal disease extent ever observed. Consequently, analyses based on automated data may exaggerate the maximal disease extent at the time of cohort entry. As part of the study, the maximal disease extent at the time of cohort entry will be ascertained from medical records. Similarly, clinic

visit dates are not stored in a longitudinal fashion. The database tracks only the date of the latest clinic visit, and the ability to address the completeness of follow-up care is therefore constrained.

- Actual drug exposure information not available
    - The actual dose and dosing scheme intended by the prescribing physician for upadacitinib treatment are not available from the data sources. Nevertheless, the recorded dispensed strength is available and will be used as a proxy for the daily dose.
    - In Sweden, only dispensed drugs are recorded on an individual level in the [redacted], while drugs administered in hospitals are not. Since information on dispensed drugs are available, primary non-adherence is not an issue. However, there is no information about actual patient consumption of the dispensed drugs.
    - In Denmark and Sweden, indication for a prescribed medication is not explicitly recorded in available data sources, therefore the use of upadacitinib among patients with UC could be in theory for other indications.
    - In Spain, treatment data are recorded through pre-defined treatment-specific data fields which are used as a proxy for actual dispensations, which are not available from [redacted]. Nevertheless, it is assumed that all recorded treatments are filled and administered as the prescribing physicians intended for diseases with a high burden if not under control (such as UC).
- In Sweden and Denmark, data in health and administrative registers are collected primarily for administrative purposes and may have limited information.
- In Sweden, there is no data for laboratory tests performed or vaccination status. In Denmark, the laboratory data stem from hospital-based laboratories, and vaccination information is limited to reimbursed vaccines.
- In Sweden and Denmark another limitation is that the diagnosis for UC will be retrieved from the [redacted] covering only patients treated in specialist care. Hence, patients diagnosed in primary care settings only may not be included in the study. Since UC is supposed to be managed by gastroenterology specialists rather than primary care physicians, and the use of the [redacted] in this study, misclassification of these patients using these data sources is unlikely [59].
- The availability of outcomes variables, will be dependent on the completeness and accuracy of coding for the covariates and proxy variables defined. Direct information on physician adherence is not available in any of the data sources.
- The presence of some of the individual risk factors defining the subgroups of higher risk are not available. Smoking status and detailed information for smoking such as years of smoking as a risk factor for malignancy and MACE, is not available in Denmark and Sweden. Proxies (smoking cessation treatment, and chronic obstructive pulmonary disease

diagnosis) can be used to assess history of smoking, but the correlation between these proxies and current or past smokers is low and therefore not judged useful to use as outcome variables. Prolonged immobilization as a risk factor for VTE is not available in any of the countries as it is usually not considered a clinical diagnosis. There is no reliable data available for assessment of periodic skin examinations in any of the countries. The sensitivity of using procedure codes to detect relevant skin examination is uncertain. In Sweden and Denmark Child-Pugh-C score is not available in the data sources.

- Limited by the nature of the data source, it is not possible to determine the opinions of prescribers including what could be considered suitable treatment alternative for each individual patient and, furthermore, whether each case upadacitinib use was due to no suitable treatment alterative available.
- Medications that are also available over the counter (e.g. NSAIDs) is likely to be under-captured.

9.10. Other aspects

Not applicable.

10. Protection of human subjects

Differences in legislation may exist across the three countries. The coordinating investigator in each country are governed by regional 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 GETECCU (the scientific society maintaining the [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 [redacted]. For the current study, some of the variables of interest (e.g., VTE risk factors, hyperlipidaemia) extend beyond the field of UC and are not routinely collected in [redacted] data. Consequently, a new informed consent form will need to be obtained for this post-authorisation safety study (PASS) for all patients who participate in the chart abstraction component of the study.

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, the investigators will adhere to commonly accepted research practices, including those described in the following guidance documents: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (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 pseudonymized 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 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 electronic health care records. This is a non-interventional study based on data previously 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 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 study progress reports and a final study report.

AbbVie will review the reports before submission to the authorities.

The study will be registered on ENCePP EU 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 the 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 [60]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Checklist will be followed [61].

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14. Annex 1. List of stand-alone documents

None

15. Annex 2. ENCePP checklist for study protocols

Study title: Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe

EU PAS Register® number: Study not yet registered
Study reference number (if applicable):

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)	☐	☐	☒	
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?	☐	☐	☒	

Comments:

Drug utilization study

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
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	☒	☐	☐	9.2
	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?	☐	☒	☐	
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?	☐	☐	☒	

Comments:

Drug utilization study

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?	☒	☐	☐	9.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
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)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

N/A since descriptive drug utilization study

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

Comments:

N/A since descriptive drug utilization study

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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.3, 9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

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)	☒	☐	☐	9.8, 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?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding?	☐	☐	☒	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Only descriptive drug utilization study

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: [redacted]

Signature: _____

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 1 Disease code and treatment code

Disease	Codes	Type of code	Register
UC	[redacted]	ICD-10	[redacted]
Upadacitinib	[redacted]	ATC	[redacted]

16.1. Variables and Operationalisation in Sweden and Denmark

Table 2 Baseline characteristics and outcome variable definitions

aRMM variable	Coding system	Codes	Register in SE and DK	Timing compared to upadacitinib	Description
Malignancy					
≥65 years of age	NA	[redacted]			
History of Malignancy	ICD-10				
MACE					
≥65 years of age	NA				
Atheroesclerosis	ICD-10				
Hypertension	ICD-10				
	ATC				I· Alpha adrenergic blockers II· Non-loop diuretics III· Vasodilators IV· Beta blockers V· Calcium channel blockers VI· Renin-angiotensin system inhibitors [redacted]

		[redacted]			
Diabetes mellitus	ICD-10	[redacted]			
	ATC				
Hyperlipidemia	ICD-10				
	ATC				
Congestive heart failure	ICD-10				
Myocardial infarction	ICD-10				cardiovascular risk factor
Stroke	ICD-10				cardiovascular risk factor
Lipid lowering drugs	ATC				
LDL, HDL, triglycerides, total cholesterol	Laboratory test				Denmark only Check for out-of-range values

GI perforations			
Diverticulitis	ICD-10	[redacted]	
Crohn's disease	ICD-10		
GI perforations	ICD-10		
NSAIDs	ATC		
Corticosteroids	ATC		
Opioids	ATC		
VTE			
VTE	ICD-10	[redacted]	Deep venous thrombosis (DVT) or pulmonary embolus (PE)

Recent major surgeries	[redacted]	Sweden. To only include major surgeries further selection of the procedure codes will be done before data extraction
		Denmark
Combined hormonal contraceptives or hormone replacement therapy		
Inherited coagulation disorder		Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and Protein S deficiency
Serious and opportunistic infections including active tuberculosis		
Hepatitis B or C	[redacted]	Additional medication conditions might be added, this will be defined in the SAP
Herpes zoster		
Chronic infection		
Active TB		

	Laboratory test	[redacted]	Laboratory test for active TB taken. Denmark only
	Mandatory reporting of contagious diseases		Sweden only
Recent Serious infection	ICD-10		Respiratory tract infections
			Infections of the gastrointestinal tract*
			Urinary tract infection
			Infections of the skin and subcutaneous tissue
			Other infections

		[redacted]		
Anti-viral therapy	ATC			
Lymphocyte	Laboratory test		[redacted]	Denmark only. Check for out-of range values
Neutrophil	Laboratory test			Denmark only Check for out-of range values
Live attenuated virus vaccine	NA	NA		Denmark only measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, influenza (intranasal), oral polio vaccine, typhoid fever if available in the Danish Health Service register

Pregnancy			
Pregnancy	NA	[redacted]	
Prescribing patterns			
≥65 years of age	NA		
Chronic kidney disease stage 3+	ICD-10		
Severe renal impairment	ICD-10		
CYP3A4 inhibitors	ATC		clarithromycin, itraconazole, ketoconazole

aRMM variable	Coding system	Codes	Register in SE and DK	Timing compared to upadacitinib	Description
Malignancy					
≥65 years of age	NA	[redacted]			
History of Malignancy	ICD-10				
MACE					
≥65 years of age	NA	[redacted]			
Atheroesclerosis	ICD-10				
Hypertension	ICD-10				
	ATC				I· Alpha adrenergic blockers II· Non-loop diuretics III· Vasodilators IV· Beta blockers V· Calcium channel blockers VI· Renin-angiotensin system inhibitors [redacted]

Diabetes mellitus	ICD-10	[redacted]	
	ATC		
Hyperlipidemia	ICD-10		
	ATC		
Congestive heart failure	ICD-10		
Myocardial infarction	ICD-10		cardiovascular risk factor
Stroke	ICD-10		cardiovascular risk factor
Lipid lowering drugs	ATC		
LDL, HDL, triglycerides, total cholesterol	Laboratory test		Denmark only Check for out-of-range values

GI perforations			
Diverticulitis	ICD-10	[redacted]	
Crohn's disease	ICD-10		
GI perforations	ICD-10		
NSAIDs	ATC		
Corticosteroids	ATC		
Opioids	ATC		
VTE			
VTE	ICD-10	[redacted]	Deep venous thrombosis (DVT) or pulmonary embolus (PE)

Recent major surgeries	KVÅ	[redacted]	Sweden. To only include major surgeries further selection of the procedure codes will be done before data extraction
	NOMESCO		Denmark
Combined hormonal contraceptives or hormone replacement therapy	ATC		
Inherited coagulation disorder	ICD-10		Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and Protein S deficiency
Serious and opportunistic infections including active tuberculosis			
Hepatitis B or C	ICD-10		Additional medication conditions might be added, this will be defined in the SAP
Herpes zoster	ICD-10		
Chronic infection	ICD-10		
Active TB	ICD-10		
	ATC		

	Laboratory test	[redacted]	Laboratory test for active TB taken. Denmark only
	Mandatory reporting of contagious diseases		Sweden only
Recent Serious infection	ICD-10		Respiratory tract infections
			Infections of the gastrointestinal tract*
			Urinary tract infection
			Infections of the skin and subcutaneous tissue
			Other infections

		[redacted]	
Anti-viral therapy	ATC		
Lymphocyte	Laboratory test		Denmark only. Check for out-of range values
Neutrophil	Laboratory test		Denmark only Check for out-of range values
Live attenuated virus vaccine	NA		Denmark only measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, influenza (intranasal), oral polio vaccine, typhoid fever if available in the Danish Health Service register

Pregnancy			
Pregnancy	NA	[redacted]	
Prescribing patterns			
≥65 years of age	NA		
Chronic kidney disease stage 3+	ICD-10		
Severe renal impairment	ICD-10		
CYP3A4 inhibitors	ATC		clarithromycin, itraconazole, ketoconazole

aRMM variable	Coding system	Codes	Register in SE and DK	Timing compared to upadacitinib	Description
Malignancy					
≥65 years of age	NA	[redacted]			
History of Malignancy	ICD-10				
MACE					
≥65 years of age	NA	[redacted]			
Atheroesclerosis	ICD-10				
Hypertension	ICD-10				
	ATC				I· Alpha adrenergic blockers II· Non-loop diuretics III· Vasodilators IV· Beta blockers V· Calcium channel blockers VI· Renin-angiotensin system inhibitors [redacted]

Diabetes mellitus	ICD-10	[redacted]	
	ATC		
Hyperlipidemia	ICD-10		
	ATC		
Congestive heart failure	ICD-10		
Myocardial infarction	ICD-10		cardiovascular risk factor
Stroke	ICD-10		cardiovascular risk factor
Lipid lowering drugs	ATC		
LDL, HDL, triglycerides, total cholesterol	Laboratory test		Denmark only Check for out-of-range values

GI perforations			
Diverticulitis	ICD-10	[redacted]	
Crohn's disease	ICD-10		
GI perforations	ICD-10		
NSAIDs	ATC		
Corticosteroids	ATC		
Opioids	ATC		
VTE			
VTE	ICD-10	[redacted]	Deep venous thrombosis (DVT) or pulmonary embolus (PE)

Recent major surgeries	KVÅ	[redacted]	Sweden. To only include major surgeries further selection of the procedure codes will be done before data extraction
	NOMESCO		Denmark
Combined hormonal contraceptives or hormone replacement therapy	ATC		
Inherited coagulation disorder	ICD-10		Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and Protein S deficiency
Serious and opportunistic infections including active tuberculosis			
Hepatitis B or C	ICD-10		Additional medication conditions might be added, this will be defined in the SAP
Herpes zoster	ICD-10		
Chronic infection	ICD-10		
Active TB	ICD-10		
	ATC		

	Laboratory test	[redacted]	Laboratory test for active TB taken. Denmark only
	Mandatory reporting of contagious diseases		Sweden only
Recent Serious infection	ICD-10		Respiratory tract infections
			Infections of the gastrointestinal tract*
			Urinary tract infection
			Infections of the skin and subcutaneous tissue
			Other infections

		[redacted]			
Anti-viral therapy	ATC				
Lymphocyte	Laboratory test				Denmark only. Check for out-of range values
Neutrophil	Laboratory test				Denmark only Check for out-of range values
Live attenuated virus vaccine	NA				Denmark only measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, influenza (intranasal), oral polio vaccine, typhoid fever if available in the Danish Health Service register

Pregnancy			
Pregnancy	NA	[redacted]	
Prescribing patterns			
≥65 years of age	NA		
Chronic kidney disease stage 3+	ICD-10		
Severe renal impairment	ICD-10		
CYP3A4 inhibitors	ATC		clarithromycin, itraconazole, ketoconazole

Baseline variables	Coding System	Codes	Register in SE and DK	Timing compared to upadacitinib	Description
Lifestyle risk factors					
Drug or alcohol abuse	ATC	[redacted]			
	ICD-10				
Smoking	ATC				identified via smoking cessation drugs N06AX12: only Zyban brand name

	ICD-10	[redacted]			COPD as a marker for smoking
Other medical history					
Chronic obstructive pulmonary disease	ICD-10	[redacted]			In addition to diagnoses, Germany might also identify patients based on participation in a specific disease management program
	ATC				COPD related medication. Further selection within R03 will be made in the SAP.
Recent gastroduodenal ulcer	ICD-10				
Inflammatory bowel disease	ICD-10				
Osteoporosis	ICD-10				
	ATC				
Anemia	ICD-10				
Malnutrition	ICD-10				
Other immune-mediated inflammatory diseases	ICD-10				(e.g. rheumatoid arthritis, atopic dermatitis)
Concomitant medication					

Biologic therapies and biosimilars	ATC (DK) Procedure code (DK)	[redacted]	(e.g., golimumab, vedolizumab, infliximab, adalimumab, ustekinumab)
Immunosuppressants	ATC		(e.g., azathioprine, cyclosporine)

16.2. Variables and Operationalisation in Spain

Table 3 Variables and Operationalisation in Spain

Variables	Description	Operationalisation
Demographics	Sex, year of birth, race/ethnicity	[redacted]
Socioeconomic factors	Education, employment status, income	
BMI	BMI (if available), weight, and height	
Disease characteristics	Date of first UC diagnosis, disease location (proctitis/left-sided colitis/ pancolitis), UC treatments before upadacitinib initiation, number of previous UC hospitalisations, IBD surgeries, and outpatient visits 5 years before initiation (including those for endoscopies, colonoscopies, and colectomies), flares of UC, and presence of a stoma at initiation or during follow-up	
Disease severity	Date of severity assessment, UC severity Mayo score, Montreal classification, stools/day, blood in stools, nocturnal stools, other severity variables	
Comorbidities	Record of moderate or severe hepatic impairment	
	Record of chronic kidney disease	
	Record of chronic obstructive pulmonary disease	
	Record of diverticular disease	

Variables	Description	Operationalisation
	Record of gastroduodenal ulcer	[redacted]
	Record of malignancy, including NMSC	
	Record of serious infection within 90 days of initiation	
	Record of anaemia	
	Record of atherosclerotic disease	
	Record of cardiovascular risk factors and cardiocerebrovascular disease, such as obesity, hypertension, diabetes mellitus, hyperlipidaemia, congestive heart failure, myocardial infarction, and stroke	
	Record of other immune-mediated inflammatory diseases	
	Record of extra-intestinal manifestations	
	Record of malnutrition	
	Record of osteoporosis	
Lifestyle factors	Record of smoking, drug abuse, and/or alcohol abuse	
Concomitant medications	Record of UC treatments	
	Record of therapy with CYP3A4 inducers	
	Record of systemic corticosteroid therapy	

Variables	Description	Operationalisation
	Record of NSAID use	[redacted]
	Record of opioid use	
	Record of combined hormonal contraceptive or hormone replacement therapy	
Laboratory tests	Record of laboratory tests for hepatic and renal function	
Severe renal impairment	Record of severe renal impairment	
Severe hepatic impairment (Child-Pugh-C)	Record of Severe hepatic impairment (Child-Pugh-C)	
Age ≥ 65 years	Record of year of birth	
Individuals receiving strong inhibitors of CYP3A4	Record of CYP3A4 use at initiation or during the study period	
Upadacitinib start date(s)	Record of written prescriptions for upadacitinib based on pre-defined treatment data field	
Upadacitinib end date(s)	Record of written prescriptions for upadacitinib based on pre-defined treatment data field	

Variables	Description	Operationalisation
Upadacitinib dose(s)	Record of written prescriptions for upadacitinib based on pre-defined treatment data field	[redacted]
Reason for discontinuation	Record of upadacitinib discontinuation	
Dosage patterns of upadacitinib	Record of written prescriptions for upadacitinib	
Serious and opportunistic infections (including TB)	Record of serious or opportunistic infection requiring hospitalisation	
Chronic infections	Record of chronic infections prior to upadacitinb initiation	
Hepatitis B and C	Record of hepatitis B or C	
Herpes zoster	Record of herpes zoster	
Active TB	Record of active TB and/or TB screening	
Live attenuated vaccines	Record of vaccination with live attenuated virus	
Lymphocyte and neutrophil counts	Record of absolute lymphocyte and absolute neutrophil counts obtained 60 days before initiation and during treatment and identification of out-of-range values	

Variables	Description	Operationalisation
Lipid levels	Record of LDL, HDL, triglycerides, and total cholesterol obtained 10–14 weeks after initiation and during treatment and identification of out-of-range values. Record of use of lipid-lowering therapies.	[redacted]
Pregnancy	Record of pregnancy at initiation of upadacitinib or during treatment and record of additional prescription(s) for upadacitinib once pregnancy is identified	
VTE (including DVT and PE)	Record of VTE before upadacitinib initiation or during treatment, recent major surgery, prolonged immobilisation, obesity	

AE = adverse event; BMI = body mass index; DVT = deep vein thrombosis; eGFR = estimated glomerular filtration rate; [redacted]; HDL = high-density lipoprotein; IBD = inflammatory bowel disease; ICD-10 = *International Classification of Diseases, 10th Revision*; LDL = low-density lipoprotein; NMSC = non-melanoma skin cancer; NSAID = nonsteroidal anti-inflammatory drug; PE = pulmonary embolism; TB = tuberculosis; UC = ulcerative colitis; VTE = venous thromboembolism.

[a] Capture as an AE if the patient is receiving an immunosuppressant or biological therapy.

[b] Obtained through review of patients' records.

Document Approval

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