# Study Protocol

## Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe



**Marketing Authorisation Holder**: AbbVie Deutschland GmbH & Co. KG (EU), AbbVie Inc (US)
**Study number:** P21-825

**PASS information**

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| **Title** | Drug Utilization Study Evaluating the Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe |
| **Protocol version identifier** | Version 3.2 |
| **Date of current version of protocol** | 10 January 2024 |
| **EU PAS register number** | TBD |
| **Active substance** | Upadacitinib (ATC code L04AA44) |
| **Medicinal product** | RINVOQ® |
| **Product reference** | EMEA/H/C/004760 |
| **Procedure number** | Not applicable |
| **Marketing authorisation holder(s)** | EU: AbbVie Deutschland GmbH & Co. KG<br>US: AbbVie Inc. |
| **Joint PASS** | No |
| **Research question and objectives** | The study aims to evaluate the use of upadacitinib (RINVOQ®) in individuals with atopic dermatitis (AD) in routine clinical care in Denmark, Germany, Spain, and Sweden. The study objectives are:<br>1. To describe the baseline characteristics of individuals with AD who are new users of upadacitinib<br>2. To the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the additional risk minimisation measures (aRMMs) among individuals with AD who are new users of upadacitinib, by:<br>a. Quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use<br>b. Quantifying the compliance to recommendations for the use among individuals who have risk factors for gastrointestinal perforation, serious infections, malignancy, major adverse cardiovascular events (MACE), and venous thromboembolic event (VTE)<br>c. Quantifying the compliance to the recommendations for the use among patients aged 65 years and older<br>d. Quantifying the compliance to the recommendations for contraindicated use including pregnancy, and active tuberculosis<br>e. Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark, Germany, and Spain only)<br>3. To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: |

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|---|---|
| | a. Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections<br>b. Describe the use of upadacitinib among patients aged 65 years and older<br>c. Describe the use of upadacitinib 30 mg |
| **Country(-ies) of study** | Denmark, Sweden, Germany, Spain |
| **Authors** | [redacted] |

**Marketing authorisation holder(s)**

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| Marketing authorisation holder (MAH) | AbbVie GmbH/AbbVie Inc. |
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**Approval Page: Centre for Pharmacoepidemiology (CPE), Karolinska Institutet**

**Project Title:** Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe

Principal Investigator: [redacted]

Version: 3.2

Version Date: 10 January 2024

[redacted] [redacted]
Date

**Approval Page: AbbVie Inc.**

**Project Title:** Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe

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|---|---|
| MAH Approver: | [redacted] PharmacoEpidemiology Center of Excellence (PeCoE), Global Epidemiology |
| Version: | 3.2 |
| Version Date: | 10 January 2024 |

[redacted] Date

# 1. Table of Contents

# 2. List of Abbreviations

| Abbreviation | Descriptions |
|---|---|
| AD | Atopic Dermatitis |
| aRMMs | Additional Risk Minimization Measures |
| ATC | Anatomical Therapeutic Chemical classification |
| CEI | Scientific Committee and Ethical Research Committee [Comité de Ética de Investigación] |
| CMBD-AH | Hospital discharge data |
| COVID-19 | Coronavirus disease 2019 |
| CPE | Centre for Pharmacoepidemiology |
| CPR | Central Pharmaceutical Reference |
| CYP3A4 | Cytochrome P450 3A4 |
| DMSc | Doctor of Medical Science |
| DSc | Doctor of Science |
| EBM | German uniform assessment standard |
| EMA | European Medicines Agency |
| EU | European Union |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| GDPR | General Data Protection Regulation |
| [redacted] | [redacted] |
| GI | Gastrointestinal |
| GM | German Modification |
| GVP | Good Pharmacovigilance Practice |
| HCP | Health Care Providers |
| HDL-C | High-Density Lipoprotein Cholesterol |
| HZ | Herpes zoster |
| ICD-10 | International Classification of Diseases, Tenth Revision |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| JAK | Janus Kinase |
| LDL-C | Low-Density Lipoprotein Cholesterol |
| LMP | Last Menstrual Period |
| MACE | Major Adverse Cardiovascular Events |
| MAH | Marketing Authorisation Holder |
| MSc | Master of Science |
| MD | Medical Doctor |
| MPH | Master of Public Health |
| MSc | Master of Science |

| | |
|---|---|
| N/A | Not Applicable |
| NPR | National Patient Register |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| OPS | Operationen- und Prozedurenschlüssel |
| PAS | Post-Authorisation Studies |
| [redacted] | [redacted] |
| PhD | Philosophie Doctor |
| PIN | Personal Identification Number |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PZN | Pharmacy identification Number |
| RA | Rheumatoid Arthritis |
| [redacted] | [redacted] |
| SAP | Statistical Analysis Plan |
| ScD | Doctor of Science |
| SHI | Statutory Health Insurance |
| [redacted] | [redacted] |
| SmPC | Summary of Product Characteristics |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| TB | Tuberculosis |
| US | United States |
| USA | United States of America |
| VTE | Venous Thromboembolic Event |
| WHO | World Health Organization |

# 3. Responsible Parties

| Parties | Name, Degree(s) | Title/Role | Affiliation | Address |
|---|---|---|---|---|
| Principal investigator | [redacted] | Associate Professor | Centre for Pharmaco-epidemiology, Karolinska Institutet | Karolinska Institutet KEP/CPE [redacted] |
| Coordinating investigators, Denmark | [redacted] | Professor | [redacted] | [redacted] |
| | [redacted] | Professor, department Chair | [redacted] | [redacted] |
| Coordinating investigator, Germany | [redacted] | Unit Head Monitoring of Drug Utilization and Safety | [redacted] | [redacted] |
| Coordinating investigator, Spain | [redacted] | Head, Real World Epidemiology (RWEpi) Research Group | [redacted] | [redacted] |
| Coordinating investigator, MAH | [redacted] | Head, PharmacoEpidemiology Center of Exellence (PeCoE), Global Epidemiology | AbbVie Inc. | Pharmacovigilance and Patient Safety 1 North Waukegan Road North Chicago, IL 60064 USA |

# 4. Abstract

**Title:**

Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe

Version 3.2, 10 January 2024

Main author: [redacted] Karolinska Institutet, Centre for Pharmacoepidemiology, KEP/CPE, [redacted]

**Rationale and background:**

Atopic dermatitis (AD) is a highly prevalent, chronic, systemic inflammatory disease causing significant physical and psychological burden, as well as significant economic impact. Upadacitinib is an oral selective and reversible inhibitor of Janus Kinase (JAK) that was approved by the European Medicines Agency (EMA) on 16 December 2019 for the treatment of moderate to severe active rheumatoid arthritis in adults and 23 August 2021 for the treatment of moderate to severe AD in patients 12 years of age and older, who are candidates for systemic therapy.

As with other JAK inhibitors also marketed in Europe, important safety risks have been identified with upadacitinib that require additional risk minimization measures (aRMMs) such as a health care provider (HCP) educational guide and a patient card as detailed in the European Union risk management plan for RINVOQ. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib warning and precautions for use have been changed and the posology has been updated in the summary of product characteristics (SmPC). In addition, gastrointestinal (GI) perforation was added as an adverse drug reaction in upadacitinib extension indication variation procedure for Crohn's disease (dated 17 February 2023). The HCP guide has been updated accordingly after these procedures and is focused on the targeted risks: malignancy, serious and opportunistic infections including tuberculosis (TB) and herpes zoster (HZ), major cardiovascular events (MACE), GI perforation, venous thromboembolic events (VTE), and fetal malformation following exposure in utero (pregnancy risk). The HCP educational guide also contains information on the upadacitinib use in patients 65 years of age or older and in atopic dermatitis with doses higher than 15 mg once daily.

Using electronic healthcare data from Denmark, Germany, Spain, and Sweden this drug utilisation study will describe baseline characteristics of individuals with AD exposed to upadacitinib, and evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs in the AD population by providing insights regarding how clinical practice patterns correspond to the listed recommendations in the SmPC and the HCP guide when using upadacitinib (RINVOQ®) for AD in routine clinical care.

**Research question and objectives:**

The study aims to evaluate the use of upadacitinib (RINVOQ®) in individuals with AD in routine clinical care in Denmark, Germany, Spain, and Sweden. The study objectives are:

1. To describe the baseline characteristics of individuals with AD who are new users of upadacitinib
2. To the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by:
    a. Quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use
    b. Quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE
    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, Germany, 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, 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 upadacitinib 30 mg

**Study design:**

The study is a drug utilization, descriptive, non-interventional, population-based, cohort study of new users of upadacitinib (RINVOQ®) for the treatment of AD identified in [redacted] from four European countries: Denmark, Germany, Spain, and Sweden.

**Population:**

The study population consists of all individuals with AD registered in the databases in the four countries who are treated with upadacitinib. Each individual will be followed from the initiation of upadacitinib to the end of the study period (i.e., 31 December 2024), study withdrawal, or death.

**Variables:**

The exposure of interest will be the use of upadacitinib.

To describe the baseline characteristics of new users of upadacitinib the study will include the baseline variables: demographics, socioeconomic factors, number of prescribed/administered AD medications in the year prior to upadacitinib initiation, number of hospitalizations and outpatient visits in the 5 years prior to upadacitinib initiation, type of prescriber of upadacitinib, lifestyle risk factors, medical history, comorbidities, as well as prior and concomitant medications.

To evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs, the study will include outcome variables related to: malignancy, MACE, GI perforation, VTE, serious and opportunistic infections including HZ, contraindications (pregnancy, and active TB) and posology.

**Data sources:**

Electronic healthcare data from Denmark, Germany, Spain, and Sweden.

**Study size:**

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

**Data Analysis:**

This will be a descriptive study. Upon upadacitinib initiation, baseline characteristics of individuals will be assessed. Proportions of the aRMM outcome variables will be assessed prior to upadacitinib initiation, at upadacitinib initiation and during continuous treatment of upadacitinib, depending on the outcome variable being reported. The proportion of the outcome variables will be calculated as the number of individuals for each specific outcome variable over the total number of individuals considered for that specific outcome. Utilization of upadacitinib will be stratified by the time period before and after the implementation of the revised aRMMs from the Article 20 referral procedure as well as by Coronavirus disease 2019 (COVID-19) pandemic time periods (COVID-19 pandemic and non-COVID-19 pandemic).

**Milestones:**

Study progress will be reported in 2024 and 2025. The final study report will be submitted to the EMA in September 2026.

# 5. Amendments and Updates

The protocol version 3.2, dated 10 January 2024, is the amended protocol addressing comments from the Pharmacovigilance Risk Assessment Committee (PRAC) rapporteur assessment of protocol version 3.1, dated 22 August 2023.

The protocol version 3.1, dated 22 August 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 3.0, dated 14 March 2023.

The protocol version 3.0, dated 14 March 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 2.0, dated 13 May 2022, including new additional risk minimization measures (aRMMs) adopted in the European Medicines Agency (EMA) procedure under Article 20 of Regulation (EC) 726/2004 (EMEA/H A20/1517/C/004760/0017, concluded 10 March 2023) and in the upadacitinib extension of indication variation updated assessment report (Procedure No. EMEA/H/C/004760/II/0027, dated 17 February 2023).

The protocol version 2.0, dated 13 May 2022, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 1.0, dated 08 November 2021.

# 6. Milestones

| **Milestone** | **Planned date** |
|---|---|
| Registration in the EU PAS register | 30 days post protocol approval |
| Start of data collection for secondary data use<br>(date when individual patient data extraction starts) | Q2 2024 |
| Study progress report 1 | Q4 2024 |
| Study progress report 2 | Q3 2025 |
| End of data collection for secondary data use<br>(date when analytical data set is available) | Q1 2026 |
| Final report of study results (incl. data up to 31 December 2024) | Q3 2026 |

# 7. Rationale and Background

Atopic dermatitis (AD) is a highly prevalent, chronic, systemic inflammatory disease causing significant physical and psychological burden, as well as significant economic impact [1 4]. The prevalence of AD is estimated at 15 30% in children and 2 10% in adults [2]. The incidence has increased in recent decades in industrialized countries [4]. Clinical features of AD include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. Pruritus is a hallmark of the condition, responsible for much of the disease burden borne by patients and their families [5]. Sleep disturbance is commonly associated with AD and stems in large part from severe pruritus [6, 7]. The diagnosis of AD is made clinically and is based on history, morphology and distribution of skin lesions, and associated clinical signs. However, AD is a heterogeneous disease with presentation varying by patient age, lesion chronicity, and flare duration.

Upadacitinib (RINVOQ®) is an oral selective and reversible inhibitor of Janus kinase (JAK) that was approved by the EMA on 16 December 2019 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs and on 23 August 2021 for the treatment of moderate to severe AD in patients 12 years of age and older, who are candidates for systemic therapy. The recommended upadacitinib dose regimens for individuals with moderate to severe AD are 15 mg and 30 mg once daily for adults and 15 mg once daily for adolescents weighing 30 kg or more and elderly patients ≥65 years of age.

As with other JAK inhibitors already marketed in Europe (tofacitinib, baricitinib, filgotinib, abrocitinib), important safety risks have been identified with upadacitinib that require aRMMs such as a health care provider (HCP) educational guide and a patient card as detailed in the European Union (EU) risk management plan for RINVOQ®. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib warnings and precautions for use have been changed and the posology has been updated in the summary of product characteristics (SmPC). In addition, gastrointestinal (GI) perforation was identified as an adverse drug reaction in upadacitinib extension indication variation procedure for Crohn's disease (dated 17 February 2023). The HCP educational guide and the patient card have been updated accordingly after these procedures and is focused on the targeted risks: malignancy, serious and opportunistic infections including herpes zoster (HZ), major cardiovascular events (MACE), GI perforation, venous thromboembolic events (VTE), and fetal malformation following exposure in utero (pregnancy risk). According to the HCP educational guide, upadacitinib is contraindicated during pregnancy and in patients with active tuberculosis (TB).

The aRMMs for upadacitinib are implemented across indications. For RA, a population-based drug utilization study to evaluate the effectiveness of initial aRMMs for upadacitinib in the treatment of RA is ongoing in a network of European RA registries, including [redacted]

This drug utilization study will describe baseline characteristics of individuals with AD exposed to upadacitinib, and evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs in the AD population by providing insights regarding how the listed recommendations correspond to clinical practice patterns when using upadacitinib (RINVOQ®) for AD in routine clinical care.

# 8. Research Question and Objectives

The study aims to evaluate the use of upadacitinib (RINVOQ®) in individuals with AD in routine clinical care in Denmark, Germany, Spain, and Sweden. The study objectives are:

1. To describe the baseline characteristics of individuals with AD who are new users of upadacitinib
2. To the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by:

a. Quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use

b. Quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE

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, Germany 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, 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 upadacitinib 30 mg

# 9. Research Methods

## *9.1. Study Design*

The study is a drug utilization, descriptive, non-interventional, population-based, cohort study of new users of upadacitinib (RINVOQ®) for the treatment of AD identified in electronic healthcare data from four European countries: Denmark, Germany, Spain, and Sweden.

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

Patient characteristics will be described at upadacitinib initiation. In addition, outcome variables among new users of upadacitinib will be assessed prior to upadacitinib initiation, at upadacitinib initiation and during continuous treatment of upadacitinib to evaluate if the important safety information communicated in the HCP educational guide is followed.

## *9.2. Setting*

The study is based on [redacted] from Denmark, Germany, Spain, and Sweden covering populations of approximately 5.8 million, 25 million, 5.8 million, and 10.2 million people, respectively. Details on the data sources are in Section 9.4.

### 9.2.1. Source Population and Study Cohort

The *source population* consists of all individuals with upadacitinib exposure registered in the data sources in the four countries.

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

- have at least one prescription/administration of upadacitinib in the *study period* (see definition in Section 9.2.2)
- be ≥ 12 years old on the date of initiation of upadacitinib
- have at least 12 months continuous residency in the respective country/region (Denmark, Sweden, or Spain) or have at least 12 months continuous insurance coverage (Germany) on the date of initiation of upadacitinib
- have a diagnosis of AD before or on the date of initiation of upadacitinib.

See Annex 3. Additional information, Table 3.1 for International Classification of Diseases, Tenth Revision (ICD-10) and Anatomical Therapeutic Chemical classification (ATC) codes and source.

### 9.2.2. Study Period

The *study period* ranges from start date of distribution of aRMM for the treatment of AD in Denmark, Germany, Spain, and Sweden (22 October 2021, 27 August 2021, 04 April 2022, and 08 September 2021, respectively) until 31 December 2024.

### 9.2.3. Follow-Up

Each individual will be followed from the initiation of upadacitinib to the end of the *study period* (i.e., 31 December 2024), study withdrawal (emigration in Denmark and Sweden, move outside Catalonia in Spain and withdrawn from the insurance in Germany) or death.

## *9.3. Variables*

### 9.3.1. Exposure

Exposure will be based on prescriptions and/or administrations of upadacitinib. In Denmark, exposure will be identified by joining administrations from the [redacted], administrations from the [redacted] and pharmacy-dispensed prescriptions from the [redacted]. In Germany, exposure will be identified by reimbursed pharmacy-dispensed prescriptions from [redacted]. In Spain, exposure will be identified through dispensed prescriptions in hospital pharmacies using the [redacted]). In Sweden, exposure will be identified through pharmacy-dispensed prescriptions from the [redacted].

Continuous treatment will be defined based on the first and subsequent prescriptions and administrations, considering the available information in each country. Details on how to join prescription and administration information will be given in the statistical analysis plan (SAP).

Treatment episodes based on prescriptions will be calculated as described in the following steps and illustrated in Figure 1:

1. All prescriptions of upadacitinib within the *study period* are identified.
2. The duration of each prescription will be calculated using the assumed daily dosage of one tablet per day. The duration of each prescription in days equals the total amount of tablets received.
3. Overlapping days of upadacitinib use will be ignored assuming that when individuals receive a new prescription of upadacitinib during the use of the previous prescription, the amount previously received would be completely used.
4. If the gap between the end date of the current prescription and the start date of the next prescription is less than or equal to 30 days, then the treatments will be considered within the same *treatment episode* and the gap will be considered exposed time. If the gap is greater than 30 days, the treatments will be considered two different *treatment episodes* and the gap will be considered unexposed time.
5. After the duration of each treatment episode is calculated, a period of 30 days (equal to the allowed gap) will be added at the end of a *treatment episode*.

Individuals will be considered as being on *continuous treatment* during each *treatment episode*. Individuals in the *study cohort* will contribute to the study with all upadacitinib *treatment episodes* until the end of the *follow-up*, and consequently they can have several periods of *continuous treatment*.

### 9.3.2. **Baseline Characterisation Variables**

To describe the baseline characteristics of individuals with AD who are new users of upadacitinib, descriptive statistics will be reported for the following baseline variables (definitions, source, codes, and look-back periods are given in Annex 3. Additional information, Table 3.2).

- Demographic variables e.g., sex, age, region of residence
- Socioeconomic factors e.g., education, employment status, income
- Number of prescribed/administered AD medications in the year prior to upadacitinib initiation
- Number of AD hospitalizations and outpatient visits in the 5 years prior to upadacitinib initiation
- Type of prescriber of upadacitinib
- Lifestyle risk factors prior to upadacitinib initiation
  - Drug or alcohol abuse (identified through proxies)
  - Smoking (identified through proxies in Denmark, Germany and Sweden)
- Medical history and comorbidities
  - Malignancy
  - Cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, myocardial infarction, and stroke
  - Atherosclerotic disease
  - Inflammatory bowel disease
  - Crohn's disease
  - Diverticular disease
  - Diverticulitis
  - VTE
  - Inherited coagulation disorder
  - Recent major surgeries
  - Recent serious infection
  - Hepatitis B or C
  - Active TB
  - HZ
  - History of chronic infection
  - Chronic kidney disease stage 3+
  - Chronic obstructive pulmonary disease
  - Gastroduodenal ulcer
- Prior and concomitant medications
  - Cytochrome P450 (CYP) 3A4 inhibitors (ketoconazole, itraconazole, clarithromycin)
  - Systemic corticosteroids
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Opioids
  - Combined hormonal contraceptives or hormone replacement therapy

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

- Individuals who are 65 years of age or older

- Individuals with risk factors for MACE and malignancy
- Individuals with severe hepatic impairment
- Individuals that are dispensed upadacitinib with a strength of 30 mg

### 9.3.3. **aRMM Outcome Variables**

To evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs the outcome variables described in the following sections will be reported (definitions, source, codes and look-back periods are given in Annex 3. Additional information, Table 3.2).

#### 9.3.3.1. Malignancy

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

- Proportion of individuals who are ≥65 years of age at upadacitinib initiation
- Proportion of individuals with current malignancy at upadacitinib initiation or a history of malignancy prior to upadacitinib initiation
- Among individuals without a history of malignancy, proportion of individuals with a diagnosis of malignancy during *continuous treatment* of upadacitinib during *follow-up*
- Among individuals with a diagnosis of malignancy during *continuous treatment* of upadacitinib during *follow-up*, proportion of individuals who continue to receive additional dispensations/administrations of upadacitinib after the diagnosis
- Proportion of individuals 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 individuals 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 for individuals with AD:

- Proportion of individuals who are ≥ 65 years of age at upadacitinib initiation
- Proportion of individuals with a history of atherosclerotic disease prior to upadacitinib initiation
- Proportion of individuals 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 individuals without a history of other cardiovascular risk factors, proportion of individuals with cardiovascular event during *continuous treatment* of upadacitinib during *follow-up*

- Among individuals with a cardiovascular event during *continuous treatment* of upadacitinib during *follow-up*, proportion of individuals who continue to receive additional dispensations/administrations of upadacitinib after the event
- Proportion of individuals 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 their patient's lipid levels during treatment with upadacitinib. To describe the number of individuals being monitored for lipid levels while being treated with upadacitinib, the following outcome variables will be included for individuals with AD:

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

#### 9.3.3.3. GI Perforation

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

- Proportion of individuals with a history of diverticulitis prior to upadacitinib initiation
- Proportion of individuals with a history of Crohn's disease prior to upadacitinib initiation
- Proportion of individuals with a recent dispensed prescription/administration of NSAIDs, corticosteroids or opioids prior to upadacitinib initiation
- Proportion of individuals with diverticulitis or GI perforation during *follow-up*

#### 9.3.3.4. Venous Thromboembolic Events

The HCP guide recommends using upadacitinib with caution if individuals are at high risk of VTE due to risk factors other than MACE or malignancy risk factors. To assess the physician adherence to the recommendation, the following outcome variables will be included for individuals with AD:

- Proportion of individuals with a history of VTE prior to upadacitinib initiation
- Proportion of individuals 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 an individual experience VTE. To assess whether this recommendation is being followed the following outcome variables will be included for individuals with AD:

- Among individuals without a history of VTE, proportion of individuals with at least one diagnosis of VTE during *continuous treatment* of upadacitinib during *follow-up*
- Among individuals with at least one diagnosis of VTE during *continuous treatment* of upadacitinib during *follow-up*, proportion of individuals with one or more dispensed prescriptions/administrations of 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 individuals with active serious infections. Active serious infection is listed as a contraindication to upadacitinib use in the SmPC. 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 HZ. The following outcome variables will be included for individuals with AD:

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

In the HCP guide physicians are recommended to screen patients before prescribing upadacitinib. The following outcome variables will be included for individuals with AD:

- Proportion of individuals with laboratory tests for absolute lymphocyte and absolute neutrophil counts in the 60 days period prior to upadacitinib initiation or during *follow-up* (Denmark, Germany, and Spain only)

- Among individuals with laboratory tests for lymphocytes and absolute neutrophil counts taken during *follow-up*, proportion of individuals with at least one value out-of-range, as assessed by the laboratory taking the laboratory test (Denmark and Spain only)
- Among individuals with a low laboratory test result 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:

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

#### 9.3.3.6. Contraindications

Contraindications to upadacitinib described in the HCP guide are pregnancy and active TB. 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 contraindicated use of upadacitinib the following outcome variables will be included for individuals with AD:

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

#### 9.3.3.7. Posology and duration of use

The HCP guide contains reminders regarding dosing specific to the AD indication and to individuals 65 years of age or older, that physicians are recommended to follow. To quantify the compliance to recommendations for posology, the following outcome variables will be included:

- Proportion of individuals ≥ 65 years of age prescribed upadacitinib with a strength of 15 mg and 30 mg

- Proportion of adolescents (from 12 to 17 years of age) prescribed upadacitinib with a strength of 15 mg and 30 mg
- Proportion of individuals with a higher risk of VTE, malignancy and MACE prescribed upadacitinib with a strength of 15 mg and 30 mg
- Proportion of individuals with severe renal impairment prescribed upadacitinib with a strength of 15 mg and 30 mg
- Proportion of individuals with a dispensed prescription/administration of strong CYP3A4 inhibitors (clarithromycin, itraconazole, ketoconazole) during *continuous treatment* of upadacitinib with a strength of 15 mg and 30 mg

Information about physician prescribed dose is not available in any of the countries so instead strength of the dispensed substance will be used. Each individual is assumed to take one tablet per day of the strength that is prescribed.

In addition, duration of use will be described categorically and continuously based on estimated *continuous treatment* (see section 9.3.1. ). The following will be reported:

- Length of continuous treatment periods categorised in ≤ 1month, > 1 month and ≤ 3 months, > 3 months and ≤ 6 months, > 6 months and ≤ 12 months, > 12 months and ≤ 24 months, > 24 months
- Mean length of continuous treatment periods
- Median length of continuous treatment periods
- Number of continuous treatment periods

Since an individual can have several periods of *continuous treatment,* an individual can contribute in the summaries several times.

## *9.4. Data Sources*

### 9.4.1. **Denmark and Sweden**

Data from the [redacted] in Denmark and Sweden will be used. In Denmark, vaccinations (only those paid by the [redacted]) will be identified using the [redacted], while laboratory tests and their results will be identified using the [redacted]. In addition, the [redacted] will be used, see Table 1 below.

The assignment of a unique personal identification numbers (PIN) to all Danish and Swedish residents at birth or upon immigration makes it possible to cross-link data between the national registers. The PIN is kept unchanged throughout life, so individuals can be followed-up throughout

their lifetime, except for migrants. The registers are updated on a yearly basis with up to 2 years production time before release to research, depending on content. The registers contain the following information:

- From the population-based registers and the [redacted] information on demographic variables, migration and socioeconomic factors will be obtained.
- The [redacted] contain information on all hospitalizations and outpatient visits to specialist care, including primary and secondary diagnoses recorded at discharge. Diagnoses for AD and other approved indications, medical history, comorbidities, and outcomes are recorded according to ICD-10.
- The national cancer registers contain information on all cancer diagnoses (morphologically verified). In addition, information about cancer diagnoses might also be obtained from the [redacted]
- The date and cause of death will be obtained from the cause of death registers. In [redacted] will be used for identifying date of death.
- The [redacted] include data on the formulations and date of all dispensed prescriptions. Drugs are categorized according to ATC codes [8]. Main exposure in Sweden will be defined based on dispensed prescriptions from the [redacted], while in Denmark exposure will be captured by the [redacted], pharmacy dispensed prescriptions in the [redacted], and by treatment codes in the [redacted]. If captured by treatment codes in the [redacted] information about dose, strength, amount dispensed will not be available.
- The medical birth registers include data on practically all deliveries in Sweden and Denmark including stillborn after gestational week 22, respectively; live deliveries are registered regardless of gestational week. 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], since 1971, 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.
- The [redacted] database includes information about reimbursed vaccines administered in primary care.

**Table 1 Data Sources in Denmark and Sweden**

| **Sweden** [redacted] | **Denmark** [redacted] |
|---|---|
| [redacted] | [redacted] |
| | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| | [redacted] |
| | [redacted] |

### 9.4.2. **Germany**

[redacted] was established and is maintained by the [redacted] is based on medical claims data from 4 German statutory health insurance (SHI) providers [redacted]. The database includes data on approximately 25 million insured people from all regions of Germany who have been insured with one of the participating providers since 2004 or later.[28] Per data year, there is information on approximately [redacted] of the general population. Preliminary analyses have shown that the database is representative of the German population. [29, 30] For each insured person, [redacted] contains demographic information; information about all hospitalisations, including in-hospital procedures (operationen- und prozedurenschlüssel [OPS] codes); information about outpatient visits with procedures (German uniform assessment standard [EBM] codes); and reimbursed outpatient dispensations. All diagnoses are coded according to ICD-10- German Modification (GM) and [redacted] captures laboratory tests performed (tests results are not captured). The contents of the linked [redacted] and of the central pharmaceutical reference (CPR) database are as follows:

- Sociodemographic data: year of birth, sex, SHI code, region of residence, nationality (German, not German, or unknown), occupational code, dates of insurance coverage (entry and exit), reasons for end of coverage (including death).
- Hospital data: admission diagnoses, secondary diagnoses and main discharge diagnoses, admission and discharge date, reason for discharge (including death), diagnostic and surgical procedures (OPS codes); hospital diagnoses are coded according to ICD-10-GM (at least 4 digits).
- Outpatient prescription drug data: pharmacy identification number (PZN), date of prescription and dispensation, physician identification number and specialty, quantity prescribed. Data on underlying medical indication are not available.

- Pharmaceutical information (from CPR): PZN, generic name, brand, manufacturer, size, strength, defined daily dose, pharmaceutical formulation, and ATC GM code.
- Outpatient medical treatment data: diagnostic certainty, dates of treatment, outpatient care/encounter codes (EBM codes, developed for payment of physicians for the outpatient treatment of German SHI patients) with exact date, and types of treatment/diagnostic procedures (OPS codes) on quarterly basis. Outpatient diagnoses are coded in ICD-10-GM (at least 4 digits) and are collected by calendar quarter; the exact dates of diagnoses are not available, but can be estimated.

The lag time from patient encounters to the incorporation of data into the database is 2 years. Data from 2021 will be included at the end of fourth quarter of 2023.

### 9.4.3. **Spain**

The [redacted] database in Catalonia, Spain, contains data from primary-care electronic medical records and other complementary databases. It is set up by the [redacted] since 2006. The database collects information from [redacted] primary health care centres and includes more than 5.8 million patients active in 2021, about [redacted] of the Catalan population. [31]

Individuals are automatically incorporated into [redacted] if they are registered in the public health system and have been assigned to a primary care centre of the [redacted]. The only requirement to do the self-registration in the public health system is to live in Catalonia (based on census certificate). Individuals can leave the database when they move out of the catchment area of [redacted] or die. [redacted] is representative of the general population living in Catalonia in terms of age, sex, and geographic distribution. [redacted] is updated on a 6-monthly basis and includes high-quality data on demographics, all-cause mortality, diseases diagnoses, prescription and dispensation of drugs in community pharmacies, laboratory tests, socio-economic indicators, vaccinations, lifestyle information, parent-child linkage and clinical parameters, among others. The linkage between [redacted] and other complementary databases through a Trusted Third Party using the individual's national security number, provides the potential to access multiple patient information. [32] In the present study, [redacted] will be linked with the following registers:

- Minimum basic set of hospital discharge data [redacted]: includes the information recorded in all Catalan public hospitals such as admission diagnoses, secondary diagnoses and main discharge diagnoses, admission and discharge date, reason for discharge, medical procedures registered during the hospitalization, among others. All diagnoses are coded according to ICD-10. [33]
- [redacted]: broad, specific, and centralized online registry for all hospitals in Catalonia designed to systematically collect information on the hospital outpatient drugs that are dispensed in hospitals and reimbursed by the Catalan Health System. [34, 35]

### *9.5. Study Size*

Not applicable since drug utilization study. All initiators of upadacitinib during the *study period*, in the AD 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 (whereby PIN has been replaced by a unique dummy identification number) from the Danish population and health registers will be provided by Statistics Denmark. The health register data will be accessed and analyzed by logging on to the Statistics Denmark Servers via a password protected role-based safe data portal.

In Germany, personal identifying data such as name, address, date of birth, and contact information are kept strictly separate from the study data. No person involved in data analysis has access to the identifying information, and no person involved in pseudonymization performs data analysis. Study data are only stored and analyzed using identification numbers (so-called pseudonyms).

In Spain, pseudonymized individual-level data will be provided by [redacted] to the research team at [redacted]. Only the research team at [redacted] will have access to the data and only aggregated results will be shared with the study team. For this study, [redacted] will be linked to [redacted] and [redacted]

In Sweden, pseudonymized data (PIN has been replaced by a unique dummy study identification number) from the Swedish health registers will be provided by the [redacted]. Population data will be provided by [redacted]. 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.

Data will be cleaned and coded, and harmonized analytic datasets will be prepared according to the specifications provided in the SAP and according to each research partners internal standard operating procedures. 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, NC, 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.

Upon upadacitinib initiation, characteristics of individuals as described in Section 9.3.2. will be assessed. Proportions of the outcome variables described in Section 9.3.3. will be assessed prior to upadacitinib initiation, at upadacitinib initiation or during *continuous treatment* of upadacitinib, depending on the outcome variable being reported. The proportion of the outcome variables will be calculated as the number of individuals for each specific outcome variable over the total number of individuals 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 selective subgroups, during Q2 2023 and the aRMMs (i.e., HCP guide and patient card) were revised accordingly. 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 GI perforation and VTE.

Therefore, the utilization of upadacitinib will be stratified by the time period before and after start date of distribution of the revised HCP guide in Denmark, Germany, Spain and Sweden (15 May 2023, pending German regulatory approval, pending Spanish regulatory approval, and 05 May 2023, respectively). 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.

To take effects of the Coronavirus disease 2019 (COVID-19) pandemic into account (see also Section 9.10. ), the utilization of upadacitinib will be stratified by COVID-19 pandemic time periods (COVID-19 pandemic and non-COVID-19 pandemic). Country specific dates for end of COVID-19 pandemic will be defined in the SAP.

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, individuals 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*

Data storage, management and analyses will be conducted according to each research partners standard operating procedures. At a minimum, the statistical analysis plan and the statistical programming and analyses will be reviewed and supervised by a senior statistician and all study documents (protocol, report, publications) will be reviewed by the entire research team. A senior epidemiologist at each research partner will supervise the project and 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, and The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. In Germany, analyses will be conducted also according to the Good Practice of Secondary Data Analysis [36], and Guidelines and Recommendations for Ensuring Good Epidemiological Practice [37].

### *9.9. Limitations of the Research Methods*

Data in health and administrative registers are collected primarily for administrative purposes and may have limited information. For Swedish, German and Spanish data, it is a limitation that only dispensed drugs are recorded on an individual level in the [redacted] the dispensation claims and the [redacted], respectively, while drugs administered in hospitals are not. Since we have information on dispensed drugs, primary non-compliance is not an issue. However, we do not know whether the individuals consume the drugs they are dispensed. Indication for medication use is not explicitly recorded in the available data sources, therefore there will be uncertainty about whether upadacitinib was given for AD or any other indication. While the dispensed strength is known, the actual dose and dosing scheme intended by the physician is unknown. In Sweden and Denmark, information on AD diagnoses is retrieved from the NPRs covering only individuals treated in specialist care. Hence, individuals diagnosed in primary care only are not included in the study in Sweden and Denmark.

The availability of capturing the outcomes of interest will be dependent on the completeness and accuracy of coding for these variables and proxy variables defined. In addition, there are no national laboratory data nor vaccine data in Sweden. In Germany, information regarding date and type of laboratory and diagnostic tests are available, but not the test results and vaccination

information is limited to reimbursed vaccines. In Denmark, the laboratory data stem from hospital-based laboratories, and vaccination information is limited to reimbursed vaccines. Different coding practices between countries may require the application of database-specific algorithms and variable definitions. Especially for [redacted], this is needed to avoid overestimation of prevalence of comorbidity.

The lower dose of upadacitinib should be used in selected risk groups according to changes in the HCP guide following Article 20 procedure in Q2 2023. The presence of some of these individual risk factors defining these subgroups of higher risk may not be available. Smoking status and detailed information for smoking such as years of smoking, as a risk factor for malignancy and MACE are not available in Denmark, Germany and Sweden. In Spain information about current and past smoker is available but not years of smoking. Immobilization as a risk factor for VTE is not available in any of the countries. Information about lactation is not available in this study. 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.

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 alternatives for each individual patient and, furthermore, whether in each case upadacitinib use was due to no suitable treatment alterative available.

### *9.10. Other Aspects*

The COVID-19 pandemic has had profound effect on availability of healthcare and regular visits to healthcare professionals might have been reduced during the pandemic. Therefore, the COVID-19 pandemic might have had an influence on the aRMM distributions and this study. The distribution of the first version of RINVOQ's aRMM for RA was completed before the World Health Organization (WHO) declaration of the COVID-19 pandemic on March 11, 2020. The aRMMs version 3.0 for the AD indication was first distributed on 22 October 2021 in Denmark, 27 August 2021 in Germany, 04 April 2022 in Spain, and 08 September 2021 in Sweden.

In Denmark, most pandemic restrictions were lifted on 01 February 2022, with authorities stating that the virus was no longer a "critical threat". Sweden abolished pandemic regulations and restrictions on 09 February 2022 and from 01 April 2022, COVID-19 was no longer classified as dangerous to the public. Germany marked the end of the COVID-19 pandemic on 05 April 2023, while Spain lifted pandemic measures on 01 March 2023. On 05 May 2023, the head of WHO declared "with great hope" an end to COVID-19 as a public health emergency. The distribution of the new aRMM after Article 20 started in May 2023 in Denmark and Sweden (still pending regulatory agency endorsement in Germany and Spain).

# 10. Protection of Human Subjects

The study is based on secondary use of collected heathcare data and will not require informed consent. Differences in legislation may exist across the four countries. The coordinating investigators in each country are governed by regional rules that guarantee the integrity of data

and the privacy of individuals.

In Denmark, 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. In Sweden, 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 [redacted] and at Karolinska Institutet, and only members of the investigator teams will have access to the data in their respective countries. In Germany, data approval from SHIs and their respective governing authorities (e.g., the Federal Insurance Office for national SHI providers) is needed, while IRB/IEC approval is not needed for studies based on [redacted] according to the Ethics Committee of the University of Bremen. In Spain, approval from the [redacted] committee is needed.

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. The data protection law in force in Spain is the regulation 2016/679 of the European Parliament and of the Council of 27 April 2016, on Data Protection, and Organic Law 3/2018 of 05 December, on the protection of personal data and guarantee of digital rights. Additionally, investigators will adhere to commonly accepted research practices, including those described in the following guidance documents: ENCePP Guide on Methodological Standards in Pharmacoepidemiology, ENCePP Code of conduct, Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

AbbVie will only get access to aggregated results, but not the individual-level data used in the study.

# 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. 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-authorisation 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-authorisation 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 European Union electronic Register of Post-Authorisation 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 from this study at scientific conferences and in peer-reviewed journals. The investigators have the right to publish the results independently of the sponsor.

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# 14. Annex 1. List of Stand-Alone Documents

Feasibility report

# 15. Annex 2. ENCePP Checklist for Study Protocols

| |
|---|
| **Study title:** Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe. |

| |
|---|
| **EU PAS Register® number:** EUPAS49233<br>**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:

| |
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| |

| **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:

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| 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:

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| |

| **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:

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| |

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.1 | Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.3 |
| 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? | ☐ | ☒ | ☐ | |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.3 |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☒ | ☐ | |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☐ | ☐ | ☒ | |

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:

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| |

| **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: | | | | |
| 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:

| |
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| |

| **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 |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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:

| |
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| |

| **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:

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| |

| **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? | ☐ | ☐ | ☒ | |
| 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:

| |
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| |

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

Comments:

| |
|---|
| |

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

Date: [redacted]

Signature: _____

# 16. Annex 3. Additional information

The tables with the variables below are preliminary. Codes and definitions will be refined and further specified in the SAP before data extraction.

**Table 3.1. Disease code and treatment code**

| Disease | Codes | Type of code |
|---|---|---|
| Atopic dermatitis | [redacted] | |
| Upadacitinib | | |

**Table 3.2. Variable definitions**

| Variable | Coding system | Codes | Timing compared to upadacitinib initiation | Description |
|---|---|---|---|---|
| **Malignancy** | | | | |
| ≥65 years of age | [redacted] | | At upadacitinib initiation | |
| Malignancy | | | History: all available look-back period prior to upadacitinib initiation<br>At upadacitinib initiation<br>During follow-up | |
| Smoking | | | History: all available look-back period prior to upadacitinib initiation<br>At upadacitinib initiation | Spain only. Smoking status available in the following categories: never, past or current smoker |
| **MACE** | | | | |
| ≥65 years of age | [redacted] | | At upadacitinib initiation | |
| Smoking | | | History: all available look-back period prior to upadacitinib initiation<br>At upadacitinib initiation | Spain only. Smoking status available in the following categories: never, past or current smoker |

| | | | |
|---|---|---|---|
| Atherosclerosis | [redacted] | History: 5 years prior to upadacitinib initiation | |
| Hypertension | | History: 5 years prior to upadacitinib initiation<br>During follow-up | <br>I· Alpha adrenergic blockers<br>II· Non-loop diuretics<br>III· Vasodilators<br>IV· Beta blockers<br>V· Calcium channel blockers<br>VI· Renin-angiotensin system inhibitors<br><br>In Germany additional variables indicating cardiovascular/coronary heart diseases related to antiplatelet therapy without acetyl salicylic acid, acetyl salicylic acid only, combination of the former two anticoagulation might be used |
| Diabetes mellitus | | History: 5 years prior to upadacitinib initiation<br>During follow-up | |
| Hyperlipidemia | | History: 5 years prior to upadacitinib initiation<br>During follow-up | |
| Congestive heart failure | | History: 5 years prior to upadacitinib initiation<br>During follow-up | |

| | | | |
|---|---|---|---|
| Myocardial infarction | [redacted] | History: 5 years prior to upadacitinib initiation<br>During follow-up | |
| Stroke | | History: 5 years prior to upadacitinib initiation<br>During follow-up | |
| Lipid lowering drugs | | During follow-up | |
| LDL-C, HDL-C, triglycerides, total cholesterol | | During follow-up | Laboratory test.<br>Not available in Sweden<br>Denmark, hospital-based laboratories only<br>Germany test taken yes/no, no results |
| **GI perforations** | | | |
| Diverticulitis | | History: 5 year prior to upadacitinib initiation<br>During follow-up | |
| Crohn's disease | | History: 5 years prior to upadacitinib initiation | |
| GI perforations | | During follow-up | |
| NSAIDs | | Recent: 30 days prior to upadacitinib | |

| | | | |
|---|---|---|---|
| Corticosteroids | [redacted] | Recent: 30 days prior to upadacitinib | |
| Opioids | | Recent: 30 days prior to upadacitinib | |
| **VTE** | | | |
| VTE | | History: 5 years prior to upadacitinib initiation<br>During follow-up | Deep venous thrombosis or pulmonary embolus |
| Recent major surgeries | | 3 months prior to upadacitinib initiation | Sweden. To only include major surgeries further selection of the procedure codes will be done before data extraction |
| | | | Denmark. |
| | | | Spain. Further selection of the procedure codes will be done before data extraction |
| Combined hormonal contraceptives or hormone replacement therapy | | TBD | In Germany contraceptives will be restricted to girls and women until the age of 22 with only very few exceptions |
| Inherited coagulation disorder | | History: 5 year prior to upadacitinib initiation | Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and Protein S deficiency |

| | | | |
|---|---|---|---|
| **Serious (in-patient diagnosis only) and opportunistic infections including active tuberculosis** | | | |
| Hepatitis B or C | [redacted] | History: 5 year prior to upadacitinib initiation<br>During follow-up | Additional medication conditions might be added, this will be defined in the SAP |
| Herpes zoster | | Active: 14 days prior to upadacitinib initiation<br>During follow-up | |
| Chronic infection | | History: 5 years prior to upadacitinib initiation | |
| ≥65 years of age | | At upadacitinib initiation | |
| Diabetes mellitus | | At upadacitinib initiation | |
| Recent serious infection | | 3 months prior to upadacitinib initiation | Respiratory tract infections |
| | | | Infections of the gastrointestinal tract* |
| | | | Urinary tract infection |

| | | | |
|---|---|---|---|
| | [redacted] | | Infections of the skin and subcutaneous tissue |
| | | | Other infections |
| Anti-viral therapy | | During follow-up | |
| Lymphocyte | | 60 days prior to upadacitinib<br>During follow-up | Laboratory test.<br>Not available in Sweden<br>Denmark, hospital-based laboratories only<br>Germany test taken yes/no, no results |
| Neutrophil | | 60 days prior to upadacitinib<br>During follow-up | Laboratory test.<br>Not available in Sweden<br>Denmark, hospital-based laboratories only<br>Germany test taken yes/no, no results |

| | | | |
|---|---|---|---|
| Live attenuated virus vaccine | [redacted] | 60 days prior to upadacitinib initiation<br>During follow-up | Not available in Sweden<br>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 as available.<br>Only reimbursed vaccines. |
| **Contraindication** | | | |
| Pregnancy | [redacted] | At upadacitinib initiation<br>During follow-up | |
| Active TB | | History: 5 years prior to upadacitinib initiation<br>During follow-up | |
| | | 1 year prior to upadacitinib initiation | |
| | | 60 days prior to upadacitinib initiation | Laboratory test for active TB taken in Denmark, Germany and Spain<br>Mandatory reporting of contagious diseases in Sweden. |
| **Posology** | | | |
| Severe renal impairment | [redacted] | At upadacitinib initiation | Chronic kidney disease stage 3+ |
| CYP3A4 inhibitors | | At upadacitinib initiation | clarithromycin, itraconazole, ketoconazole |

| Baseline characteristics | | | |
|---|---|---|---|
| Drug or alcohol abuse | [redacted] | History: 5 years prior to upadacitinib initiation | |
| | | History: 5 years prior to upadacitinib initiation | |
| Smoking | | History: 5 years prior to upadacitinib initiation | identified via smoking cessation drugs<br>N06AX12: only Zyban brand name |
| | | History: 5 years prior to upadacitinib initiation | COPD as a marker for smoking |
| | | History: all available look-back period prior to upadacitinib initiation<br>During follow-up | In Spain, smoking status is categorized into the following categories: never, past or current smoker |
| Chronic obstructive pulmonary disease | | History: 5 years prior to upadacitinib initiation | In addition to diagnoses, Germany might also identify patients based on participation in a specific disease management program |
| | | History: 1 year prior to upadacitinib initiation | COPD related medication. Further selection within R03 will be made in the SAP. |
| Gastroduodenal ulcer | | History: 3 months prior to upadacitinib initiation | |

| | | | |
|---|---|---|---|
| Inflammatory bowel disease | [redacted] | History: 5 years prior to upadacitinib initiation | |

# Document Approval

Study P21825 - Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe - Version 3-2 - 10Jan2024

**Version:** 1.0 **Date:** [redacted] **Company ID:** [redacted]

| Signed by: | Date: | Meaning of Signature: |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |