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)
Study number: P21-825

PASS information

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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: 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 additional risk minimisation measures (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 gastrointestinal perforation, serious infections, malignancy, major adverse cardiovascular events (MACE), and venous thromboembolic event (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 tuberculosis 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
Country(-ies) of study	Denmark, Sweden, Germany, Spain
Authors	[redacted]

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GRS = Global Regulatory Strategy; MAH = Marketing Authorization Holder; UK = United Kingdom

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

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[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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Version: 3.3

Version Date: 13 March 2026

[redacted]

Date

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2. List of Abbreviations

Abbreviation	Descriptions
AbbVie	AbbVie Inc.
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
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPE	Centre for Pharmacoepidemiology
CPR	Central Pharmaceutical Reference
CYP3A4	Cytochrome P450 3A4
DALYS	Disability-Adjusted Life Years
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
GePaRD	German Pharmacoepidemiological Research Database
GI	Gastrointestinal
GM	German Modification
GRS	Global Regulatory Strategy
GVP	Good Pharmacovigilance Practice
HCP	Health Care Providers
HDL-C	High-Density Lipoprotein Cholesterol
HRQoL	Health-Related Quality of Life
HZ	Herpes zoster
ICD-10	International Classification of Diseases, Tenth Revision
ICS	Catalan Institute of Health [Institut Català de la Salut]
IDIAPJGol	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
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
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MPH	Master of Public Health
MSc	Master of Science
N/A	Not Applicable
NNH	Number needed to harm
NPR	National Patient Register
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OPS	Operationen- und Prozedurenschlüssel
PAS	Post-Authorisation Studies
PASS	Post-authorization safety study
PDR	Prescribed Drug Register
PhD	Philosophie Doctor
PIN	Personal Identification Number
PRAC	Pharmacovigilance Risk Assessment Committee
PZN	Pharmacy identification Number
Q	Quarter
QALYs	Quality-Adjusted Life Years
RA	Rheumatoid Arthritis
RPT-MHDA	Patient and Hospital Outpatient Drugs Treatment Registry
RWEpi	Real World Epidemiology
SAP	Statistical Analysis Plan
ScD	Doctor of Science
SHI	Statutory Health Insurance
SIDIAP	the Information System for the development of Research in Primary Care [Sistema d'Informació per el Desenvolupament d´Investigació en Atenció Primària]
SmPC	Summary of Product Characteristics
SMINET	National system for communicable disease surveillance in Sweden
SMR	Danish National Hospital Medication Register [Sygehusmedicinregisteret]
TB	Tuberculosis
UK	United Kingdom
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
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4. Abstract

Title:

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

Version 3.3, 13 March 2026

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

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 electronic healthcare data 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 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 2027.

5. Amendments and Updates

Number and date	Section of study protocol	Amendment or update	Reason
Version 3.3, 13 March 2026	4. Abstract & 6. Milestones	Date for final study report changed from Q3 2026 to Q3 2027	To be able to include data from Germany up until 31 December 2024 in the final study report. Addressing the comment from the Pharmacovigilance Risk Assessment Committee (PRAC) rapporteur assessment of the 2025 progress report, dated 27 August 2025 (Procedure No. EMEA/H/C/004760/EMA/PAM/0000 301869, dated 29 January 2026)
	4. Abstract & 9.3.2. Baseline Characteri-sation Variables	During SAP development, variable list and definitions were further refined leading to the following variable changes: 1. Removal of Number of AD outpatient visits as a proxy for AD disease characteristics 2. Removal of the socioeconomic factors Employment status and Income 3. Removal of the variable Drug or alcohol use 4. Addition of GI perforation, Ulcerative colitis and other autoimmune conditions as medical history and comorbidity 5. Redefinition of Severe renal impairment as chronic kidney disease stage 4+ instead of chronic kidney disease stage 3+ 6. Inclusion of Severe hepatic impairment as a baseline variable instead of as a sub-group	1. Deemed as an unreliable proxy after consultation with clinicians in Sweden and Germany 2. Not feasible to measure in some of the participating countries due to General Data Protection Regulation (GDPR) 3. Deemed as an unreliable proxy and removed to avoid misclassification and misinterpretation 4. To further characterize the AD population using upadacitinib 5. Chronic kidney disease stage 3 indicates moderate kidney damage [1] 6. Considering the low number of individuals expected to have severe hepatic impairment, subgroup analyses would not be feasible
	9.3.3.4. Venous Thrombo-embolic Events	"Proportion of individuals with use of combined hormonal contraceptives or hormone replacement therapy during continuous treatment of upadacitinib during follow-up" has been added as an outcome variable	The change was made to be consistent with the Rinvoq HCP guide. Combined hormonal contraceptives or hormone replacement therapy is a risk factor for VTE and should therefore be used with caution, together with upadacitinib
	9.3.3.5. Serious and Opportunistic Infections	"Proportion of individuals with a serious infection during continuous treatment of upadacitinib during follow-up" has been added as an outcome variable	The change was made to be consistent with the Rinvoq HCP guide. Actions should be taken if a patient develops a serious infection during treatment
	9.7.1. Descriptive Analysis & 9.10. Other Aspects	Dates for aRMMs distribution added	Distribution have now taken place in all countries

Number and date	Section of study protocol	Amendment or update	Reason
	16. Annex 3. Additional information	1. Codes for upadacitinib updated 2. The aRMMs variable list has been updated	1. ATC code for upadacitinib has changed and a Danish procedure code has been allocated since last protocol version 2. To reflect the changes made to the protocol as well as any refinements of codes made during statistical analysis plan development

AD = Atopic Dermatitis; aRMMs = Additional Risk Minimization Measures; ATC = Anatomical Therapeutic Chemical classification; GDPR = General Data Protection Regulation; GI = Gastrointestinal; HCP = Health Care Providers; PRAC = Pharmacovigilance Risk Assessment Committee; Q = Quarter; SAP = Statistical Analysis Plan; VTE = Venous Thromboembolic Event

The protocol version 3.2, dated 10 January 2024, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 3.1, dated 14 December 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 (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 (date when analytical data set is available)	Q1 2027
Final report of study results (incl. data up to 31 December 2024)	Q3 2027

EU = European Union; PAS = Post-Authorisation Studies; Q = Quarter

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 [2-5]. The prevalence of AD is estimated at 15-30% in children and 2-10% in adults [3]. The incidence has increased in recent decades in industrialized countries [5]. 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 [6]. Sleep disturbance is commonly associated with AD and stems in large part from severe pruritus [7, 8]. 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 DANBIO (Denmark), ARTIS (Sweden), BSRBR (UK), IOBADASER (Spain), and RABBIT (Germany).

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 Danish and Swedish nationwide registers.

In Germany, data will be collected from the German Pharmacoepidemiological Research Database (GePaRD). In Spain, data will be collected from the Information System for the development of Research in Primary Care [Sistema d'Informació per el Desenvolupament d'Investigació en Atenció Primària] (SIDIAP).

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 electronic healthcare data 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 Section 16 (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

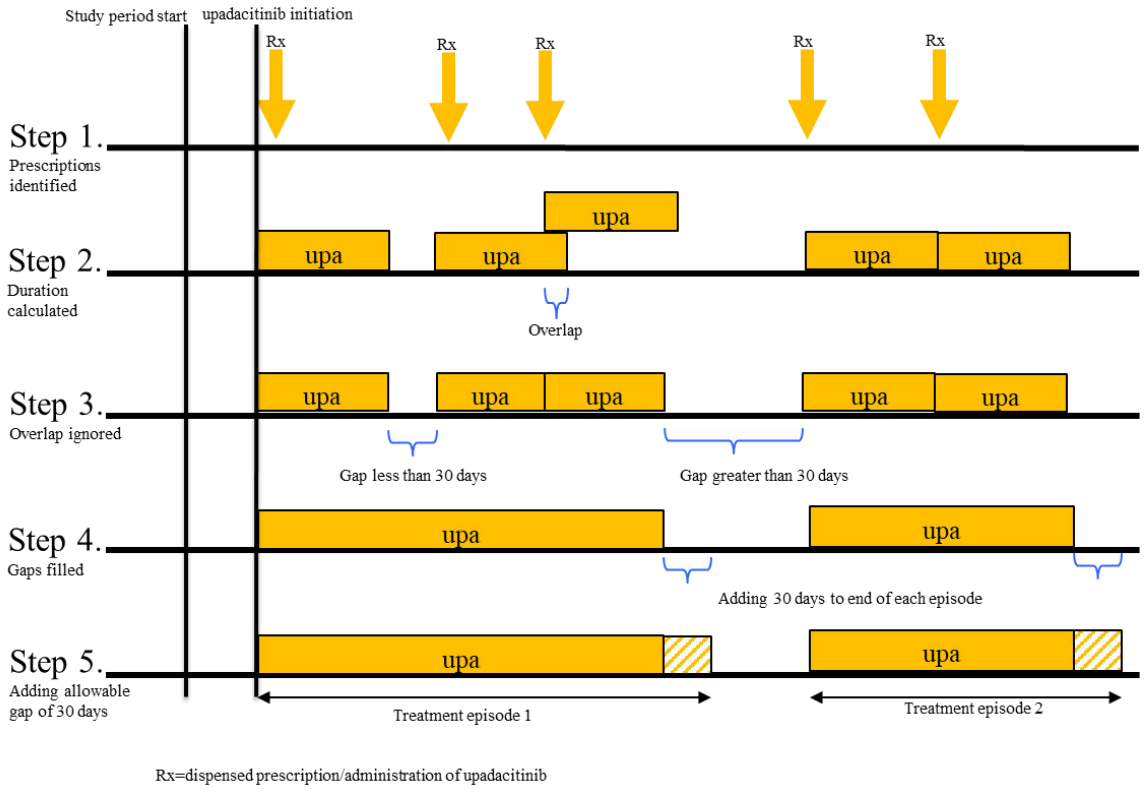
Exposure will be based on prescriptions and/or administrations of upadacitinib. In Denmark, exposure will be identified by joining administrations from the Danish National Hospital Medication Register [Sygehusmedicinregisteret] (SMR), administrations from the Danish National Patient Register (NPR) and pharmacy-dispensed prescriptions from the Danish National Prescription Registry. In Germany, exposure will be identified by reimbursed pharmacy-dispensed prescriptions from GePaRD. In Spain, exposure will be identified through dispensed prescriptions in hospital pharmacies using the Patient and Hospital Outpatient Drugs Treatment Registry (RPT-MHDA, its Catalan acronym). In Sweden, exposure will be identified through pharmacy-dispensed prescriptions from the Swedish National Prescribed Drug Register (PDR).

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*.

Figure 1. Calculation of treatment episodes



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 Section 16 (Annex 3). Additional information, Table 3.2).

- Demographic variables e.g., sex, age, region of residence
- Socioeconomic factors e.g., education
- Number of prescribed/administered AD medications in the year prior to upadacitinib initiation
- Number of AD hospitalizations in the 5 years prior to upadacitinib initiation
- Type of prescriber of upadacitinib
- Lifestyle risk factors prior to upadacitinib initiation
  - 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
  - Other autoimmune conditions
  - Atherosclerotic disease
  - Inflammatory bowel disease
  - Crohn's disease
  - Diverticular disease
  - Diverticulitis
  - GI perforation
  - VTE
  - Inherited coagulation disorder
  - Recent major surgeries
  - Recent serious infection
  - Hepatitis B or C
  - Active TB
  - Ulcerative colitis
  - HZ
  - History of chronic infection
  - Chronic kidney disease stage 4+
  - Chronic obstructive pulmonary disease
  - Gastroduodenal ulcer
  - Severe hepatic impairment
- 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 that are dispensed upadacitinib with a strength of 30 mg

9.3.3. aRMMs 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 Section 16 (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 use of combined hormonal contraceptives or hormone replacement therapy during continuous treatment of upadacitinib during follow-up
- 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.*
  - Proportion of individuals with a serious infection 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 Swedish PDR, the Danish National Prescription Registry, the Danish SMR, the NPRs, the national cancer registers, the cause of death registers, the medical birth registers, and the population-based registers in Denmark and Sweden will be used. In Denmark, vaccinations (only those paid by the National Health Service) will be identified using the Danish National Health Service Database and/or via ATC codes in the Danish National Prescription Registry, while laboratory tests and their results will be identified using the nationwide Laboratory Research Database. In addition, the Danish Educational and Socioeconomic Registries and the National System for Communicable Disease Surveillance in Sweden (SMINET) 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 Danish Educational and Socioeconomic Registries information on demographic variables, migration and socioeconomic factors will be obtained.
- The NPRs 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 NPRs.
- The date and cause of death will be obtained from the cause of death registers. In Denmark Civil Registration System will be used for identifying date of death.
- The Swedish PDR and the Danish National Prescription Registry include data on the formulations and date of all dispensed prescriptions. Drugs are categorized according to ATC codes [9]. Main exposure in Sweden will be defined based on dispensed prescriptions from the PDR, while in Denmark exposure will be captured by the Danish SMR, pharmacy dispensed prescriptions in the Danish National Prescription Registry, and by treatment codes in the Danish NPR. If captured by treatment codes in the Danish NPR 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 SMINET, 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 Danish National Health Services database includes information about reimbursed vaccines administered in primary care.

Table 1. Data Sources in Denmark and Sweden

Sweden National Registers	Denmark National Registers
Population-based registers from Statistics Sweden	Danish Civil Registration System[10] [11]
	Danish Educational and Socioeconomic Registries [12]
Swedish National Patient Register [13]	Danish National Patient Register [14]
Swedish Prescribed Drug Register [15]	Danish National Prescription Registry [16-18]
Swedish Cancer Register [19]	Danish Cancer Register [20, 21]
Swedish Cause of Death Register [22]	Danish Cause of Death Register [23]
Swedish Medical Birth Register [24]	Danish Medical Birth Register [24]
SMINET [25]	Danish National Hospital Medication Register [26]
	Nationwide Laboratory Research Database [27]
	Danish National Health Service Database [28]

SMINET = National system for communicable disease surveillance in Sweden

9.4.2. Germany

German Pharmacoepidemiological Research Database was established and is maintained by the Leibniz Institute for Prevention Research and Epidemiology – BIPS. German Pharmacoepidemiological Research Database is based on medical claims data from 4 German statutory health insurance (SHI) providers (AOK Bremen/Bremerhaven, DAK-Gesundheit, hkk

Handelskrankenkasse, and Die Techniker Krankenkasse). 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.[29] Per data year, there is information on approximately 20% of the general population. Preliminary analyses have shown that the database is representative of the German population. [30, 31] For each insured person, GePaRD 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 GePaRD captures laboratory tests performed (tests results are not captured). The contents of the linked GePaRD 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 is 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 SIDIAP database in Catalonia, Spain, contains data from primary-care electronic medical records and other complementary databases. It is set up by the Institute of Research in Primary Care (Institut D'Investigació en Atenció Primària) and Catalan Institute of Health [Institut Català de la Salut] (ICS) since 2006. The database collects information from 328 primary health care centres and includes more than 5.8 million patients active in 2021, about 75% of the Catalan population. [32]

Individuals are automatically incorporated into SIDIAP if they are registered in the public health

system and have been assigned to a primary care centre of the ICS. 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 SIDIAP or die. SIDIAP is representative of the general population living in Catalonia in terms of age, sex, and geographic distribution. The Information System for the development of Research in Primary Care [Sistema d'Informació per el Desenvolupament d´Investigació en Atenció Primària] 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 SIDIAP and other complementary databases through a Trusted Third Party using the individual's national security number, provides the potential to access multiple patient information. [33] In the present study, SIDIAP will be linked with the following registers:

- Minimum basic set of hospital discharge data (CMBD-AH): 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. [34]
- RPT-MHDA: 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. [35, 36]

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 SIDIAP to the research team at IDIAPJGol. Only the research team at IDIAPJGol will have access to the data and only aggregated results will be shared with the study team. For this study, SIDIAP will be linked to CMBD-AH and RPT-MHDA through the Data Analytics Program for Research and Innovation in Health (PADRIS; https://aquas.gencat.cat/ca/fem/intelligencia-analitica/padris/index.html).

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 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.

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, 03 November 2023, 19 Sepember 2023, 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 [37], and Guidelines and Recommendations for Ensuring Good Epidemiological Practice [38].

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 Swedish PDR, the dispensation claims and the RPT-MHDA register, 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 GePaRD, 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, in September 2023 in Spain, and in November 2023 in Germany.

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 Statistics Denmark 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 GePaRD according to the Ethics Committee of the University of Bremen. In Spain, approval from the Scientific Committee and Ethical Research Committee [Comité de Ética de Investigación] (CEI) of IDIAPJGol 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 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?	☐	☒	☐	

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:

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:

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:

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?	☐	☐	☒	
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: 13 March 2026

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	L20	ICD-10
Upadacitinib	L04AA44, L04AF03 BWHP107	ATC Danish procedure code

ATC = Anatomical Therapeutic Chemical classification; ICD-10 = International Classification of Diseases, Tenth Revision

Table 3.2. Variable definitions

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
Malignancy				
≥65 years of age	N/A	N/A	At upadacitinib initiation	
Malignancy	ICD-10	C00-C97	History: 5-years before or on index date At upadacitinib initiation During follow-up	
Smoking	N/A	N/A	Past or current smoker	Spain only. Smoking status available in the following categories: never, past or current smoker
MACE				
≥65 years of age	N/A	N/A	At upadacitinib initiation	
Smoking	N/A	N/A	Past or current smoker	Spain only. Smoking status available in the following categories: never, past or current smoker
Atherosclerotic disease	ICD-10	I20-I25, I60-I66, G45, I69, I70-I72, I738, I739, I74, I771	History: 5 years prior to upadacitinib initiation	

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
Hypertension	ICD-10	I10, I11, I12, I13, I15	History: 5 years prior to upadacitinib initiation During follow-up	
	ATC	I: C02A, C02B, C02C II: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52 III: C02DB, C02DD, C02DG, C04, C05 IV: C07 V: C07F, C08, C09BB, C09DB VI: C09		I· Alpha adrenergic blockers II· Non-loop diuretics III· Vasodilators IV· Beta blockers V· Calcium channel blockers VI· Renin-angiotensin system inhibitors 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	ICD-10	E10, E11, E12, E13, E14	History: 5 years prior to upadacitinib initiation During follow-up	
	ATC	A10		
Hyperlipidemia	ICD-10	E78	History: 5 years prior to upadacitinib initiation During follow-up	
	ATC	C10AA		
Congestive heart failure	ICD-10	I50, I11.0, I13.0, I13.2, I51.7, I25.5, I42, I43	History: 5 years prior to upadacitinib initiation During follow-up	

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
Myocardial infarction	ICD-10	I21	History: 5 years prior to upadacitinib initiation During follow-up	
Stroke	ICD-10	I60 - I64	History: 5 years prior to upadacitinib initiation During follow-up	
Lipid lowering drugs	ATC	C10AA, C10AB, C10AC, C10AD, C10AX	During follow-up	
LDL-C, HDL-C, triglycerides, total cholesterol	N/A	N/A	During follow-up	Laboratory test. Not available in Sweden Denmark, hospital-based laboratories only Germany test taken yes/no, no results
GI perforations				
Diverticulitis	ICD-10	K57	History: 5 year prior to upadacitinib initiation During follow-up	
Crohn's disease	ICD-10	K50	History: 5 years prior to upadacitinib initiation	
GI perforations	ICD-10	K22.3, K251, K252, K255, K256, K261, K262, K265, K266, K271, K272, K275, K276, K281, K282, K285, K286, K570, K572, K574, K578, K631	During follow-up	

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
NSAIDs	ATC	M01A, N02BA	Recent: 30 days prior to upadacitinib During follow-up	
Systemic Corticosteroids	ATC	C05AA, H02, J01XC, M01BA, N02CB,	Recent: 30 days prior to upadacitinib During follow-up	
Opioids	ATC	N02A	Recent: 30 days prior to upadacitinib During follow-up	
VTE				
VTE	ICD-10	I26, I801, I802, I803, I808, I809, I822, I823, I828, I829, O871, O882, T828	History: 5 years prior to upadacitinib initiation During follow-up	Deep venous thrombosis or pulmonary embolus
Recent major surgeries	KVÅ/NOMESCO/ICD-10_PCS	Any surgical procedure code associated with an in-patient hospitalization.	Recent: 3 months prior to upadacitinib initiation	
Combined hormonal contraceptives or hormone replacement therapy	ATC	G02B, G03	Recent: 6 months prior to upadacitinib initiation During follow-up	In Germany contraceptives will be restricted to girls and women until the age of 22 with only very few exceptions
Inherited coagulation disorder	ICD-10	D682, D688, D685A (DK), D685B (DK) D685E (DK), D685F (DK), D685K (DK)	History: 5 year prior to upadacitinib initiation	Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and Protein S deficiency

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
Serious (in-patient diagnosis only) and opportunistic infections				
Hepatitis B or C	ICD-10	B16, B180, B181, B171, B182	History: 5 year prior to upadacitinib initiation During follow-up	Additional medication conditions might be added, this will be defined in the SAP
Herpes zoster	ICD-10	B02	Active: 90 days prior to upadacitinib initiation During follow-up	
Chronic infection	ICD-10	A15, A16, A17, A18, A19, A30, A31, B18, B20-B24 K230, K930, M863, M864, M865, M866, M869, M900	History: 5 years prior to upadacitinib initiation	
≥65 years of age	N/A	N/A	At upadacitinib initiation	
Diabetes mellitus	ICD-10	E10, E11, E12, E13, E14	At upadacitinib initiation	
	ATC	A10		
Recent serious infection	ICD-10	H70, A361, J0, J02, A360, J03, A362, J04-J05, J37, A36.8-A36.9, J06, J36, A48.1, B01.2, J12-J18, J10.0, A37, A42.0, J20-J22, J85, J86, H66	3 months prior to upadacitinib initiation During follow-up	Respiratory tract infections
		A00-A09 (but not A02.1), K830 (but not K830F and K830G), K650, B15, K750, A42.1		Infections of the gastrointestinal tract*
		N10, N30.0, N41.0, N39.0		Urinary tract infection

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
		A46, B35-B36, L02-L03, L04, B02, B00, A60, H19.1, B01, L05, A36.3, L00, L01.0, L08, L30.3		Infections of the skin and subcutaneous tissue
		A40, A41, A32.7, A02.1, B37.7, A39.2, N70.0, N71.0, N72, A50-A53, A54, A55-A56, B30, H00.0, H03.0-H03.1, H06.1, H10.0, H10.5-H10.8, M00-M01, M60.0, M86, G00-G02, G04-G06, A39.0, A32.1, A87, B00.3-4, B01.0, B02.1, B05.1, B06.0, A83, A15-A29, A31-A32, A34-A35, A38.0, A42.2-A44, A48.0, A48.2-A49, A65-A69, A75-A79, A80-A99, B05-B06, B08-B09, B26-B27, B33-B34, B25, B37-B49, B59, B50-B83, A07.2, B99.9		Other infections
Anti-viral therapy	ATC	J05AB01, J05AB09, J05AB11	During follow-up	
Lymphocyte	N/A	N/A	60 days prior to upadacitinib During follow-up	Laboratory test. Not available in Sweden Denmark, hospital-based laboratories only Germany test taken yes/no, no results
Neutrophil	N/A	N/A	60 days prior to upadacitinib During follow-up	Laboratory test. Not available in Sweden Denmark, hospital-based laboratories only Germany test taken yes/no, no results

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
Live attenuated virus vaccine	N/A	N/A	60 days prior to upadacitinib initiation During follow-up	Not available in Sweden 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. Only reimbursed vaccines.
Contraindication				
Pregnancy	N/A	N/A	At upadacitinib initiation During follow-up	
Active TB	ICD-10	A15-A19	90 days prior to upadacitinib initiation During follow-up	
	ATC	J04AK, J04AM	90 days prior to upadacitinib initiation During follow-up	
	N/A	N/A	60 days prior to upadacitinib initiation	Laboratory test for active TB taken in Denmark, Germany and Spain Mandatory reporting of contagious diseases in Sweden.
Posology				
Severe renal impairment	ICD-10	N18.4, N18.5, Y841, Z49, Z992	5 years prior to upadacitinib initiation	Chronic kidney disease stage 4+ Country specific procedure codes will also be used.

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
CYP3A4 inhibitors	ATC	L01XX77, J05AE08, J05AR15, J05AR23, L01ED02, J01FA09, A02BD14, V03AX03, J05AR14, J05AR09, J05AR18, J05AR22, J05AE10, J05AR26, L01EM01, J05AE02, J02AC02, D01AC08, G01AF11, H02CA03, J02AB02, H02CA04, A16AX20, J05AR10, G03XB01, G03XB51, N06AX06, J05AE04, J05AP52, J05AP53, J02AC04, J05AE03, J05AE01, L01EH03, J02AC03, J01FA15, J05AE30	30 days prior to upadacitinib initiation During follow-up	
Baseline characteristics				
Smoking	ATC	N07BA, N06AX12	History: 5 years prior to upadacitinib initiation	identified via smoking cessation drugs N06AX12: only Zyban brand name
	ICD-10	J41, J43, J44, Z720, Z716, T652, F17	History: 5 years prior to upadacitinib initiation	Proxies for smoking
	N/A	N/A	Past or current	In Spain, smoking status is categorized into the following categories: never, past or current smoker

Variable	Coding system	Codes	Timing compared to upadacitinib initiation	Description
Chronic obstructive pulmonary disease (COPD)	ICD-10	J43, J44	History: 5 years prior to upadacitinib initiation	(Germany: excluding J43.0 - McLeod Syndrome, J43.1 - Panlobular emphysema)
	ATC	R03A, R03BB, R03C, R03DX07	History: 5 years prior to upadacitinib initiation	In Germany: ATC (in combination with an outpatient diagnosis) or enrolment in the disease management program "COPD" for at least one day
Gastroduodenal ulcer	ICD-10	K25, K26, K27, K28	History: 5 years prior to upadacitinib initiation	
Inflammatory bowel disease	ICD-10	K50, K51	History: 5 years prior to upadacitinib initiation	

ATC = Anatomical Therapeutic Chemical classification; COPD = Chronic obstructive pulmonary disease; CYP3A4 = Cytochrome P450 3A4; GI = Gastrointestinal; HDL-C = High-Density Lipoprotein Cholesterol; ICD-10 = International Classification of Diseases, Tenth Revision; LDL-C = Low-Density Lipoprotein Cholesterol; MACE = Major Adverse Cardiovascular Events; N/A = Not Applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; SAP = Statistical Analysis Plan; TB = Tuberculosis; VTE = Venous Thromboembolic Event

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: 3.3

Version Date: 13 March 2026

[redacted] _____ [redacted]
Date

Document Approval

Study P21825 - Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe - Protocol Version 3-3 - 13Mar2026

Version: 1.0 **Date:** 23-Mar-2026 **Company ID:** [redacted]

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