**Study Protocol**

# Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

**Marketing Authorisation Holder**: AbbVie GmbH (EU), AbbVie Inc (US)
**Study number:** P20-390

**PASS information**

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| **Title** | Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden |
| **Protocol version identifier** | Version 4.0 |
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| **Active substance** | Upadacitinib (ATC code L04AA44) |
| **Medicinal product** | Rinvoq® |
| **Product reference** | EMEA/H/C/004760 |
| **Procedure number** | EMEA/H/C/004760/MEA/013.1 |
| **Marketing authorisation holder(s)** | EU: AbbVie Deutschland GmbH & Co. KG<br>US: AbbVie Inc. |
| **Joint PASS** | No |
| **Research question and objectives** | The purpose of this study is to evaluate and characterise the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib, as described in the European Union Risk Management Plan for upadacitinib for the treatment of atopic dermatitis (AD).<br><br>**The primary objectives are**<br>• to assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline<br>• to describe the incidence of the following safety outcomes in adolescent and adult individuals with AD treated with upadacitinib:<br>o Malignancy excluding non-melanoma skin cancer (NMSC), including malignancy by type<br>o NMSC<br>o Major adverse cardiovascular events (MACE)<br>o Venous thromboembolic event (VTE)<br>o Serious infections (incl. opportunistic infections [OI])<br>o Herpes zoster (HZ)<br>o Eczema herpeticum/Kaposi's varicelliform eruption (EH/KVE)<br>o Active tuberculosis (TB)<br>o Gastrointestinal (GI) perforation<br>o Drug-induced liver injuries (DILI)<br>o Fractures<br>o All-cause mortality<br>• If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other select systemic AD treatments.<br><br>**The secondary objectives are:**<br>To describe the incidence of the safety outcomes mentioned under |

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| | primary objectives in upadacitinib users by:<br>• dose of upadacitinib (15 mg and 30 mg)<br>• age group (adolescents 12-17 years, 18-64 years, 65-74 years and ≥ 75 years) at the time of upadacitinib initiation<br>• history of moderate hepatic impairment at the time of upadacitinib initiation<br>• history of chronic infection with hepatitis B virus or hepatitis C virus at the time of upadacitinib initiation<br>• history of severe renal impairment at the time of upadacitinib initiation<br><br>If a suitable comparator is identified: to describe the incidence of the safety outcomes mentioned under primary objectives in adolescents and adult individuals with AD treated with other select systemic AD treatments by:<br>• age group (adolescents 12-17 years, 18-64 years, 65-74 years and ≥ 75 years) at the time of treatment initiation<br>• history of moderate hepatic impairment at the time of treatment initiation<br>• history of chronic infection with hepatitis B virus or hepatitis C virus at the time of treatment initiation<br>• history of severe renal impairment at the time of treatment initiation |
| **Country(-ies) of study** | Denmark, Sweden |
| **Authors** | [redacted] |

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**Approval Page: Centre for Pharmacoepidemiology, Karolinska Institutet**

**Project Title:** Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

Principal Investigator: [redacted]

Version: 4.0

Version Date: 21 March 2023

[redacted]

**Approval Page: AbbVie Inc.**

**Project Title:** Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

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| Sponsor Approver: | [redacted] PharmacoEpidemiology Center of Excellence (PeCoE), Global Epidemiology |
| Version: | 4.0 |
| Version Date: | 21 March 2023 |

[redacted] Date

## 1. Table of Contents

## 2. List of Abbreviations

| Abbreviations | Descriptions |
|---|---|
| AD | Atopic dermatitis |
| ATC | Anatomical Therapeutic Chemical classification |
| AE | Adverse event |
| CI | Confidence intervals |
| CV | Cardiovascular |
| DDD | Defined Daily Dose |
| DILI | Drug-induced liver injury |
| DMSc | Doctor of Medical Science |
| DSc | Doctor of Science |
| EH | Eczema herpeticum |
| EMA | European Medicines Agency |
| EU | European Union |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| FDA | U.S. Food and Drug Administration |
| GDPR | General Data Protection Regulation |
| GI | Gastrointestinal |
| GVP | Good Pharmacovigilance Practice |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HR | Hazard ratio |
| HZ | Herpes zoster |
| ICD-10 | International Classification of Diseases, Tenth Edition |
| IEC | Independent Ethics Committee |
| IL | Interleukin |
| IPTW | Inverse Probability of Treatment Weighting |
| IRB | Institutional Review Board |
| JAK | Janus kinase |
| KI | Karolinska Institutet |
| KVE | Kaposi’s varicelliform eruption |
| LL | Lower limit |
| MACE | Major adverse cardiovascular events |
| MD | Doctor of Medicine |
| MPH | Master of Public Health |
| MSc | Master of Science |
| NMSC | Non-melanoma skin cancer |
| OI | Opportunistic infections |
| PAS | Post-approval studies |
| PhD | Doctor of Philosophy |
| PIN | Personal identification numbers |
| PY | Person-years |
| SAP | Statistical Analysis Plan |
| ScD | Doctor of Science |
| TB | Tuberculosis |

| | |
|---|---|
| UL | Upper limit |
| VTE | Venous thromboembolic event |
| WHO | World Health Organization |

## 3. Responsible Parties

| Parties | Name, Degree(s) | Title/Role | Affiliation | Address |
|---|---|---|---|---|
| Principal investigator | [redacted] | Assoc. Professor | Centre for Pharmaco-epidemiology, Karolinska Institutet | Karolinska Institutet KEP/CPE Karolinska University Hospital Solna T2:02, 171 76 Stockholm, Sverige |
| Coordinating investigators, Denmark | [redacted] | Professor | Department of Clinical Epidemiology, Aarhus University | [redacted] |
| | [redacted] | Professor, department Chair | Department of Clinical Epidemiology, Aarhus University | [redacted] |
| Coordinating investigator, MAH | [redacted] | Head, Pharmaco-Epidemiology Center of Excellence (PeCoE), Global Epidemiology | AbbVie, Inc. | Pharmacovigilance and Patient Safety<br>1 North Waukegan Road North Chicago, IL 60064, USA |

## 4. Abstract

**Title:**

Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden

Version 4.0, 14 March 2023

Main author: [redacted] Karolinska Institutet, Centre for Pharmacoepidemiology, Karolinska Sjukhuset, T2:02, 171 76 Stockholm, Sverige

**Rationale and background:**

Atopic dermatitis (AD) is a chronic, systemic inflammatory skin disease causing significant physical and psychological burden, as well as significant economic impact. Upadacitinib is an oral selective and reversible inhibitor of Janus Kinase-1 (JAK1).

Upadacitinib doses of 15 mg and 30 mg are approved to be used in the EU for treatment of adults with moderate to severe AD. Upadacitinib 15 mg is approved to be used in the EU for treatment of adolescents with moderate to severe AD who weigh 30 kg or over. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib recommended use and doses have been changed. Upadacitinib 15 mg is approved to be used in the EU for

treatment of elderly patients ≥65 years of age or patients with risk factors for malignancy, MACE or VTEs. In addition, upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors.

As with other JAK inhibitors also marketed in Europe, important potential safety risks have been identified for the JAK class. Such safety risks include malignancy, serious and opportunistic infections including TB and HZ, fetal malformation (pregnancy risk), MACE, VTE, GI perforation and fractures.

As clinical development programs are often not designed to assess differences in relatively uncommon safety events, the safety profile needs to be complemented with data from studies in a real-world setting. From a clinical and safety perspective, it is important to gain knowledge of these and other safety concerns for upadacitinib in comparison with other relevant treatment alternatives for AD. A long-term safety study will therefore be conducted to assess the long-term safety of upadacitinib use in patients with AD in a real-world setting.

**Research question and objectives:**

The purpose of this study is to evaluate and characterise the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib, as described in the EU RMP for upadacitinib for the treatment if AD.

**The primary objectives are**

To assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline.

To describe the incidence of the following safety outcomes in adolescent and adult individuals with AD treated with upadacitinib:

- Malignancy (excluding NMSC), including malignancy by type
- NMSC
- MACE
- VTE
- Serious infections (incl. OI)
- HZ
- EH/KVE
- Active TB
- GI perforation
- Drug-induced liver injuries
- Fractures
- All-cause mortality

If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other select systemic AD treatments

**The secondary objectives are:**

To describe the incidence of the safety outcomes mentioned under primary objectives in upadacitinib users by:

- dose of upadacitinib (15 mg and 30 mg)
- age group (adolescents 12-17 years, 18-64 years, 65-74 years and ≥ 75 years) at the time of upadacitinib initiation
- history of moderate hepatic impairment at the time of upadacitinib initiation
- history of chronic infection with hepatitis B virus or hepatitis C virus at the time of upadacitinib initiation
- history of severe renal impairment at the time of upadacitinib initiation

If a suitable comparator is identified: to describe the incidence of the safety outcomes mentioned under primary objectives in adolescent and adult individuals with AD treated with other select systemic AD treatments by:

- age group (adolescents 12-17 years, 18-64 years, 65-74 years and ≥ 75 years) at the time of treatment initiation
- history of moderate hepatic impairment at the time of treatment initiation
- history of chronic infection with hepatitis B virus or hepatitis C virus at the time of treatment initiation
- history of severe renal impairment at the time of treatment initiation

**Study design:**

The study is a longitudinal, non-interventional, population-based, register-based cohort study of adolescents and adults with AD exposed to upadacitinib or other selected systemic AD treatments, identified in the Danish and Swedish nationwide registers.

A *new user,* active comparator design will be used to address the objectives of the study. *New user* is defined as not having used that specific drug substance in the year (12 months, 365 days) before the first eligible treatment.

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

**Population:**

The source population will be all individuals with at least one diagnosis of AD as registered in the national patient registers in Sweden and Denmark. To enter the study cohorts each individual will also need to have at least one dispensed prescription/administration of upadacitinib or one of the other select systemic AD treatments (except for other JAKi) during the study period.

**Variables:**

The main exposure of interest will be the use of upadacitinib. Other select systemic AD treatments may consist of azathioprine, ciclosporin, dupilumab, methotrexate and mycophenolate mofetil. The

variables studied as outcomes will be malignancy (excluding NMSC) including malignancy by type, NMSC, MACE, VTE, serious infections (including OI), HZ, EH/KVE, active TB, GI perforations, DILI, fractures, and all-cause mortality. In addition to exposures and outcomes, other baseline variables, possible confounders and effect modifiers will be included in the study. These variables will include demographics, socioeconomics, proxy measures for lifestyle factors, comorbidities, past and present medication use, and past medical procedures. As a proxy measure of disease severity, healthcare utilization before cohort entry will be considered.

**Data sources:**

Linked data from the national health and population registers in Denmark and Sweden.

**Study size:**

[redacted]

Since the potential available number of patients exposed to upadacitinib and other select systemic treatments in the first five accrual years in the national registers in Denmark and Sweden is higher than the required target number of patients for the estimated sample size for the most important outcomes and additional patients will be included into the study after the first five years, these data sources are considered sufficient for this study.

The number of individuals exposed to upadacitinib and other select systemic AD treatments will be monitored annually. If the number of upadacitinib users does not reach 50% of the target sample

size by year 2024 (captured in the progress report in 2026), additional data sources will be considered to be added to the study.

**Data Analysis:**

The labeling updates due to the Article 20 procedure pose distinct challenges for the long-term safety study in atopic dermatitis (AD). First, patients treated with upadacitinib will be expected to differ from other select systemic treatments in baseline risk factors for major cardiovascular events (MACE), malignancy and/or venous thromboembolic events (VTE), based on the updated section 4.4 (Special warnings and precautions for use) of the RINVOQ Summary of Product Characteristics (SmPC). Second, high risk patients treated with upadacitinib will likely be those with "no suitable treatment alternatives" and be more likely to have failed other therapies, not responded to the lower dose of upadacitinib, and have higher disease burden. Third, the anticipated lower incidence of safety outcomes in low-risk patients raises feasibility concerns, particularly as these relate to precision requirements for comparative analyses.

To inform comparability across treatment cohorts following the referral procedure, descriptive analyses will be conducted to characterize the users (e.g., demographics, co-morbidities and use of other medications, AD treatment experience, healthcare utilization at baseline) and the real-world utilization of upadacitinib other select systemic treatments for AD, overall and separately by country, dose (upadacitinib), age group, and relevant risk factor strata (e.g.; malignancy, MACE, VTE). Propensity scores (PS) will be generated for upadacitinib users and other select systemic AD treatments users. The distribution/overlap of propensity scores will be examined to assess the balance across cohorts. The standardized mean difference (SMD) will be used to assess comparability across treatment groups if needed.

Person-years at risk and the number of safety outcomes for upadacitinib will be reported overall and across risk factor strata, crude incidence rates for upadacitinib will be presented. [redacted] crude incidence rates for all safety outcomes will be provided for other select systemic AD treatments, as well.

[redacted]

comparisons of rates of safety outcomes between upadacitinib and comparator cohorts will be made with Cox proportional hazard regression models using appropriate strategies such as inverse probability of treatment weighting (IPTW), PS matching/ stratification/ adjustments or others to achieve comparable balance across cohorts.

Sensitivity analyses for malignancies (excluding NMSC, NMSC) and subgroup analyses of all outcomes for cohorts in the secondary objectives will be conducted as well.

**Milestones:**

Study progress will be reported every year from 2023 to 2031, except for the year of the interim report. The interim report of study results will be submitted to the EMA in 2028 and the final study report will be submitted to the EMA in 2033.

## 5. Amendments and Updates

The protocol version 4.0, dated 21 March 2023, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 3.0, dated 30 August 2022, including comments on the impact of the Article 20 referral procedure outcome on upadacitinib users.

The protocol version 3.0, dated 30 August 2022, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 2.0, dated 19 April 2022.

The protocol version 2.0, dated 19 April 2022, is the amended protocol addressing comments from the PRAC rapporteur assessment of protocol version 1.0, dated 08 November 2021.

## 6. Milestones

| Milestones | Planned Dates |
|---|---|
| Registration in the EU PASS Register | 30 days post protocol approval |
| Start of data collection for secondary data use (date when individual patient data extraction starts) | Q1 2024 |
| Annual Progress Reports[1] | Q3 2023 - Q3 2031 (except 2028) |
| Interim report of study results (incl. data up to Dec 2026) | Q4 2028 |
| End of data collection for secondary data use (date when analytical data set is available) | Q4 2032 |
| Final report of study results (incl. data up to Dec 2031) | Q4 2033 |

[1] First progress report in Q3 2023 will only include data from Sweden, and will be based on descriptive statistics ordered from the Swedish National Board of Health and Welfare. No individual data will be extracted for the 1st progress report. Data extraction is planned for Q1 2024 in both Denmark and Sweden, post EMA approval of protocol revisions following Article 20 referral procedure recommendation (10 March 2023), in due time for the 2nd progress report

## 7. Rationale and Background

Atopic dermatitis (AD) is a common chronic relapsing inflammatory skin disease. A defective skin barrier with an abnormal immunological response appears to be caused by a combination of genetic and environmental factors [1, 2]. The prevalence of AD is estimated as 15-30% in children and 2-10% in adults [2]. In adolescents, the prevalence of AD has been described to range from 1.8% in Lithuania to 15% or higher in Denmark, Bulgaria, Finland, and Hungary. Among adults, the prevalence of AD has been described to range from 2.2% in Switzerland to 17.6% in Estonia [3], and the estimated prevalence in US adults is 7.3%. Approximately 30% to 66% of patients with AD have moderate to severe active disease depending on the measures of disease activity used [4-6]. Moderate to severe disease manifests as a debilitating, itchy skin eruption leading to a significant physical, psychological, and economic burden [7].

Patients with atopic dermatitis may suffer from medical complications. Bacterial infection or dysbiosis, such as with Staphylococcus aureus, may cause exacerbations [1, 8, 9]. There is also an increased risk of viral infection such as with viral warts and molluscum contagiosum, as well as with herpes simplex (eczema herpeticum) and eczema vaccinatum [10, 11]. AD is also associated with ichthyosis vulgaris [12]. Eye complication like atopic keratoconjunctivitis and cataract can

develop in young adults [13], and children with severe AD may experience growth retardation [14, 15]. AD is also associated with food allergies and other atopic and non-atopic comorbidity conditions like autoimmune diseases [1].

Basic therapy for AD includes the use of emollients containing urea, which can improve the skin barrier function [2]. Bacterial colonization can be reduced by topical antiseptics such as triclosan or chlorhexidine [2]. Topical therapies that are used also include steroids, such as hydrocortisone ointment, or moderately potent steroids. For infected eczema, topical antiseptics may be used. Oral antibiotics may be given for infected exacerbations. Some patients with AD may be treated with phototherapy. For pruritus, sedative antihistamines may be given at bedtime, to reduce scratching (e.g. alimemazine and promethazine). Admission to hospital may be needed for the treatment of eczema herpeticum where acyclovir may be given.

To reduce inflammation in the skin, either pimecrolimus or tacrolimus can be used for topical treatment. They are calcineurin inhibitors that affect inflammatory dendritic epidermal cells and are recommended as second line treatment due to safety reasons [2]. When using anti-inflammatory treatments, combined therapy with emollients should be used. In rare instances oral corticosteroids may be used for the treatment of exacerbation of AD [2]. For very severe cases of AD, cyclosporin A may be used [2]; however, there are side effects including renal toxicity that may lead to hypertension and renal impairment. Another drug sometimes used for severe AD is azathioprine. However, side effects include myelo-suppression, hepatotoxicity, gastrointestinal disturbances, increased risk of infections and possibly skin cancer.

More recently, subcutaneous, oral and topic biologic drugs have been introduced for clinical use in AD. In 2017, the monoclonal antibody dupilumab was approved in the US and EU for adults with moderate to severe AD. Dupilumab binds to interleukin-4 (IL-4) receptors which are involved in signaling pathways relevant for the development of AD [16]. Abrocitinib was approved for adults with moderate to severe AD in the EU in December 2021. Moreover, additional drugs may come to be introduced to the market (e.g., crisaborole, nemolizumab) [17, 18].

Upadacitinib is an oral selective and reversible inhibitor of JAK1. Upadacitinib doses of 15 mg and 30 mg are approved to be used in the EU for treatment of adults with moderate to severe AD. Upadacitinib 15 mg is approved to be used in the EU for treatment of adolescents with moderate to severe AD who weigh 30 kg or over. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib recommended use and doses have been changed. Upadacitinib 15 mg is approved to be used in the EU for treatment of elderly patients ≥65 years of age or patients with risk factors for malignancy, major adverse cardiovascular events (MACE) or venous thromboembolic events (VTEs). In addition, upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors.

As with other JAK inhibitors also marketed in Europe, important potential safety risks have been identified for the JAK class. Such safety risks include malignancy, serious and opportunistic

infections including tuberculosis (TB) and herpes zoster (HZ), fetal malformation (pregnancy risk), MACE, VTE, gastrointestinal (GI) perforation and fractures.

From a clinical and safety perspective, it is important to gain knowledge of these and other safety concerns for upadacitinib, and if feasible, to provide comparisons with other relevant treatment alternatives for AD. To achieve this, data from real-world settings are needed [19].

This long-term safety study will therefore be conducted to assess the long-term safety of upadacitinib use in patients with AD in a real-world setting.

## 8. Research Question and Objectives

The purpose of this study is to evaluate and characterise the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib, as described in the EU RMP for upadacitinib for the treatment of AD.

**The primary objectives are:**

To assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline.

To describe the incidence of the following safety outcomes in adolescent and adult individuals with AD treated with upadacitinib:

- malignancy (excluding NMSC), including malignancy by type
- NMSC
- MACE
- VTE
- serious (in-patient) infections (incl. OI)
- HZ
- EH/ KVE
- active TB
- GI perforation
- DILI
- fractures
- all-cause mortality

If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other select systemic AD treatments.

**The secondary objectives are:**

To describe the incidence of the safety outcomes mentioned under primary objectives in upadacitinib users by:

- dose of upadacitinib (15 mg and 30 mg)

- age group (adolescents 12-17 years, 18-64 years, 65-74 years and ≥ 75 years) at the time of upadacitinib initiation
- history of moderate hepatic impairment at the time of upadacitinib initiation
- history of chronic infection with hepatitis B virus or hepatitis C virus at the time of upadacitinib initiation
- history of severe renal impairment at the time of upadacitinib initiation

If a suitable comparator is identified: To describe the incidence of the safety outcomes mentioned under primary objectives in adolescent and adult individuals with AD treated with other select systemic AD treatments by:

- age group (adolescents 12-17 years, 18-64 years, 65-74 years and ≥ 75 years) at the time of treatment initiation
- history of moderate hepatic impairment at the time of treatment initiation
- history of chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) at the time of treatment initiation
- history of severe renal impairment at the time of treatment initiation

## 9. Research Methods

### *9.1. Study Design*

The study is based on data from the nationwide health and administrative registers from Denmark and Sweden, covering country populations of approximately 5.8 million and 10.2 million people, respectively. It is a longitudinal, non-interventional, population-based, register-based cohort study of adolescents and adults with AD exposed to upadacitinib or other select systemic AD treatments, identified in the Danish and Swedish nationwide registers.

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

The select systemic AD treatments (including biosimilars) evaluated as potential comparator treatments in the study are:

- Azathioprine
- Ciclosporin
- Dupilumab
- Methotrexate
- Mycophenolate mofetil

ATC codes and procedure codes for the comparator treatments are listed in Annex 3. Additional Information, Table 3.2. Additional upcoming marketed AD treatments may become relevant as comparator treatments as the study progresses. Therefore, the list may be extended to cover

other available and approved AD treatments in Sweden and Denmark during the study period. Final codes and definitions will be specified in the Statistical Analysis Plan (SAP) before data extraction for interim analysis and final analysis.

A *new user,* active comparator design will be used to address the objectives of the study. *New user* is defined as not having used that specific drug substance in the year (12 months, 365 days) before the first eligible treatment.

The first dispensed prescription/administration date of upadacitinib or one of the comparator treatments within the study period (see definition in Section 9.2.2. ), will be defined as the *index date*.

## *9.2. Setting*

### 9.2.1. Source Population, Study Population and Study Cohort

The *source population* will be all individuals with at least one diagnosis of AD (ICD-10 code L20) as registered in the Danish and Swedish patient registers since 1998 (the year when ICD-10 was fully implemented in both countries).

To be eligible for inclusion into the *study population* and the *study cohorts* individuals must:

- have a recorded diagnosis of AD
- have at least one dispensed prescription/administration of upadacitinib or one of the select systemic AD treatments within 12 months from the AD diagnosis during the *study period* (see definition in Section 9.2.2. )
- be a *new user* of either upadacitinib or one of the select systemic ADtreatments at *index date*
- be ≥ 12 years old at the *index date*
- have at least 12 months' continuous residency in the respective country (Denmark or Sweden) prior to the *index date*
- For the potential comparator cohorts, have at least one dispensed prescription/administration of another systemic AD treatment before *index date*

The following exclusion criteria apply to the study population:

- Individuals who used other JAK inhibitors (e.g. tofacitinib, baricitinib, abrocitinib) at any time (all available lookback time) before the *index date* will be excluded

### 9.2.2. Study Period

The *study period* ranges from first authorization date of upadacitinib for the treatment of AD in Denmark and Sweden (23 August 2021) until 31 December 2031.

Individuals initiating one of the treatments under study will be included through the whole *study period*. To allow for at least 5 years follow-up time for malignancy excluding NMSC and NMSC, for these outcomes the population will be restricted to individuals included up until 31 December 2026.

#### 9.2.3. Follow-Up

Each individual will be followed specifically for each outcome of interest, from the *index date* to the earliest occurrence of the specific outcome of interest, end of the study period, emigration, death or initiation of any other JAK inhibitor.

### *9.3. Variables*

#### 9.3.1. Exposure

Exposure will be based on dispensed prescriptions/administrations of either upadacitinib or other select systemic AD treatments. Three exposure definitions will be used, an intention to treat (ITT), a modified ITT with censor at switch, and a time-varying exposure as described below.

*ITT exposure definition*

With the ITT exposure definition, individuals will be considered exposed to the first eligible treatment received, from *index date* until the *end of follow-up*. Individuals will only contribute person-time to one treatment.

*Modified ITT exposure definition*

With the modified ITT exposure definition, individuals will be considered exposed to the first eligible treatment received, from *index date* until *end of follow-up* but in addition censored at treatment switch. Individuals will only contribute person-time to one treatment.

*Time-varying exposure definition*

For the time-varying exposure definition, treatment episodes will be constructed as described in the following steps and illustrated in Figure 1:

1. All dispensed prescriptions/administrations of upadacitinib and comparator treatment within the *study period* are identified.
2. The duration of each dispensed prescription/administration of upadacitinib and the systemic comparator treatments will be calculated using the assumed daily dosage, i.e., the duration of each dispensed prescription/administration in days equals the total amount of treatment received divided by the assumed daily dosage.
3. If the next dispensed prescription/administration of the same treatment is before the calculated end date of the current dispensed prescription/administration the overlap will be ignored, assuming that the amount previously received would be completely used.
4. If the gap between the end date of the current dispensed prescription/administration and the start date of the next dispensed prescription/administration with the same treatment 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.
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*.

6. If a dispensed prescription/administration of another study treatment starts at the same date or during the *treatment episode* of one of the study treatments, the overlapping days between treatments will be categorized as "concomitant use/switch".
7. Periods of time without any of the studied treatments will be categorized as "unexposed time".

With the time-varying exposure definition individuals may change exposure status during *follow-up* depending on the treatment received, hence individuals will contribute person-time to several treatments.

### 9.3.2. Outcomes

The outcomes will be first event of:

- Malignancy (excluding NMSC), including malignancy by type
- NMSC
- MACE
- VTE

- Serious (in-patient) infections (incl. OI)
- HZ
- EH/KVE
- Active TB
- GI perforations
- DILI
- Fractures
- All-cause mortality

Incident malignancies will be identified via the linked national cancer registers and the national patient registers in each country. The other outcomes will be captured through inpatient and specialist outpatient diagnoses, as reflected in the national patient registers, in each country. Details on the coding, definitions, history exclusion look-back periods and source of the outcomes are listed in Annex 3. Additional Information, Table 3.3.

**Risk window for all outcomes except Malignancy excluding NMSC and NMSC**

The risk window will be from the *index date* until *end of follow-up* for the ITT exposure definition, while for the time-varying exposure definition, where the exposure status may change over time, the risk window will depend on exposure status as illustrated in Figure 1, including also non-exposed time.

**Risk window for Malignancy excluding NMSC and NMSC outcomes**

The risk window will start from a lag-time of 12 months after *index date* until the *end of follow-up* for the ITT and modified ITT exposure definitions. Events occurring during the lag-time will not be counted, instead they will be counted as medical history. Similarly, the follow-up included in the lag-time will be disregarded. Sensitivity analyses with 0- and 6-months lag time will be conducted.

### 9.3.3. Baseline Variables

In addition to exposures and outcomes, other variables that are recorded in the national registers will be included in this study. These variables will include demographic and socioeconomic measures (e.g., age, sex, region of residency, education, income, occupation, country of origin), proxy measures for lifestyle factors (e.g., smoking, alcohol use), comorbidities, past and present medication use, and prior medical procedures. As a proxy measure of disease severity, healthcare utilization within one year before cohort entry will be studied.

A list of baseline variables is presented in Table 1. In general, one-year look-back period prior to *index date* will be used for medication use and disease severity proxies and five years for all the other variables.

**Table 1 Baseline Variables**

| Data type | Description |
|---|---|
| Demographics and socioeconomics | Age<br>Sex<br>Education<br>Income<br>Occupation<br>Region of residency |
| Lifestyle factors | Smoking (identified through proxies)<br>Alcohol use (identified through proxies) |
| Medical history within 5 years prior to *index date* | Asthma<br>Obesity<br>Hypertension<br>Hyperlipidemia<br>Diabetes<br>Myocardial infarction<br>Stroke<br>Peripheral vascular disease<br>Rheumatoid arthritis<br>Depression<br>Anxiety<br>Insomnia<br>Chronic obstructive pulmonary disease (COPD)<br>Moderate hepatic impairment<br>Serious infection<br>Active TB<br>Atherosclerotic cardiovascular disease<br>Malignancy<br>Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)<br>Severe renal impairment<br>Endogenous uveitis<br>Nephrotic syndrome<br>Transplantation (organ/bone marrow)<br>Psoriasis<br>Crohn's disease<br>Ulcerative colitis<br>Celiac disease<br>Acute lymphocytic leukemia (ALL)<br>Systemic lupus erythematosus (SLE)<br>Polymyositis and dermatomyositis<br>Pemphigus<br>Polyarteritis nodosa<br>Autoimmune hemolytic anemia<br>Chronic Idiopathic (Immune) Thrombocytopenic Purpura<br>Polyarticular Severe Active Juvenile Idiopathic Arthritis<br>External Otitis<br>Previous fracture |
| Medication use within 1 year prior to *index date* | Antihypertensives<br>Lipid-lowering drugs<br>Antidepressants<br>Anxiolytic drugs<br>Antipsychotics<br>Insomnia medications |

| | |
|---|---|
| Use of AD treatments other than the ones being studied within 1 year prior to *index date* | Biologic<br>Non-biologic systemics<br>Phototherapy<br>Topical agents |
| Healthcare utilization as proxies of AD severity within 1 year prior to *index date* | Number of AD inpatient days at baseline<br>Number of AD outpatient visits at baseline<br>Number of non-AD inpatient days at baseline<br>Number of non-AD outpatient visits at baseline |

### *9.4. Data Sources*

Data from the national patient registers, the national prescribed drug registers, the national cancer registers, the cause of death registers and the population-based registers in Denmark and Sweden will be used. In addition, the Danish Hospital Medicines Register (if available at the time of data extraction) and the Danish Educational and Socioeconomic Registries will be used.

The assignment of 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 within each country. 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 two years production time before released to research, depending on content. The registers contain the following information:

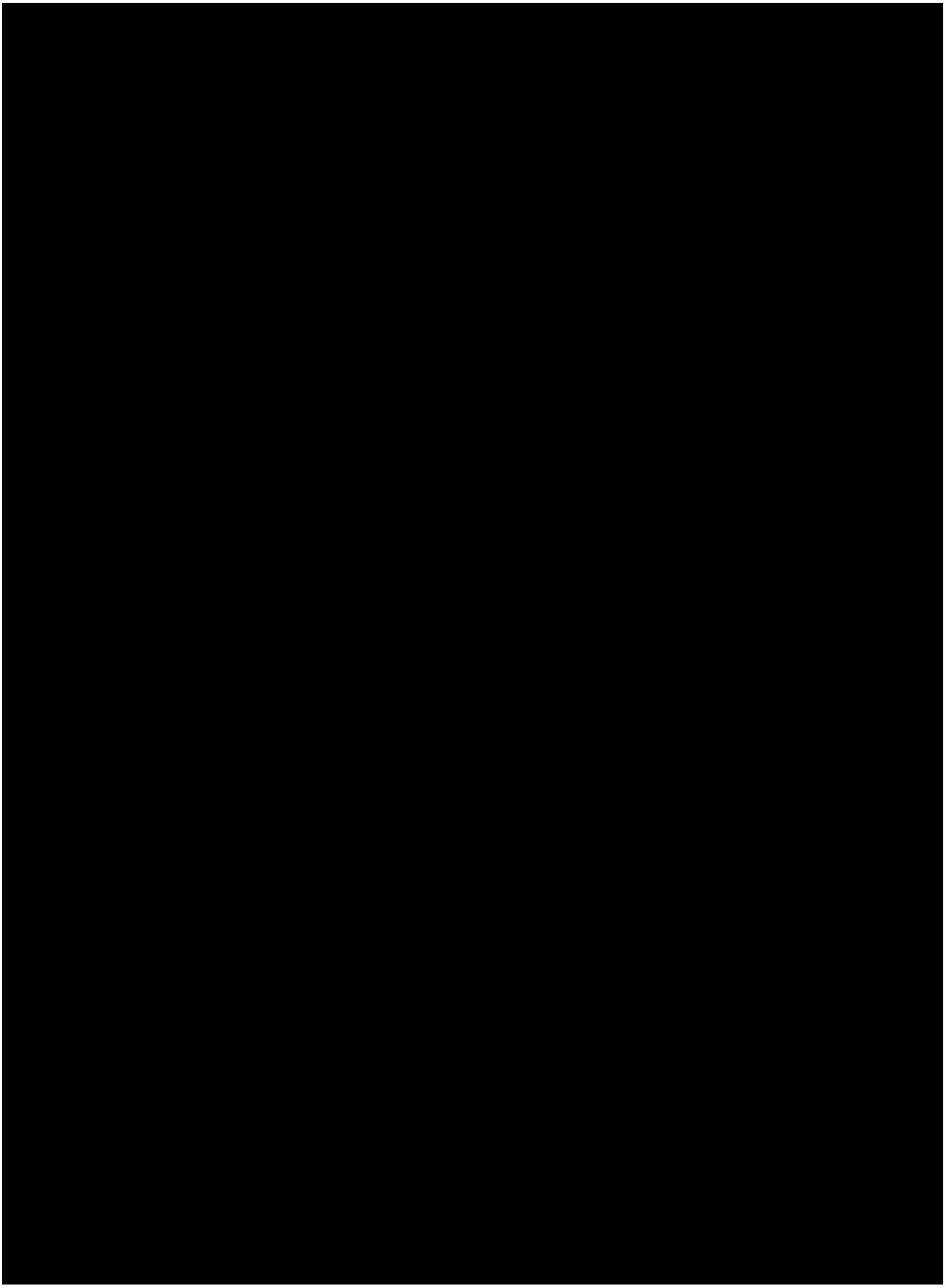
- From the population-based registers and the Danish Educational and Socioeconomic Registries information on demographic variables, migration and socioeconomic factors will be obtained.
- The national patient registers contain information on all hospitalizations and outpatient visits to specialist care, including primary and secondary diagnoses recorded at discharge. Diagnoses of AD, medical history, comorbidities, and outcomes are recorded according to the International Classification of Diseases, revision 10 (ICD-10).
- The national cancer registers contain information on all incident cancer diagnoses (morphologically verified). In addition, information about cancer diagnoses might also be obtained from the national patient registers.
- 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 prescribed drug registers include data on the formulations and date of all dispensed prescriptions. Drugs are categorized according to the WHO Anatomical Therapeutic Chemical classification system (ATC codes) [20]. Main exposure in Sweden will be defined based on dispensed prescriptions from the prescribed drug register for all treatments, while in Denmark exposure will be captured by treatment codes in the patient register and dispensed prescriptions in the prescribed drug register. When captured by treatment codes in the patient register information about dose, strength, amount dispensed will not be available. If available, Danish Hospital Medicines Registry might be used in addition. This data source is currently undergoing testing and may become available in 2023.
- The contagious disease register, since 1971, provides events reported according to the Swedish Communicable Diseases Act and the communicable diseases ordinance on diseases e.g. TB that have mandatory reporting in Sweden.

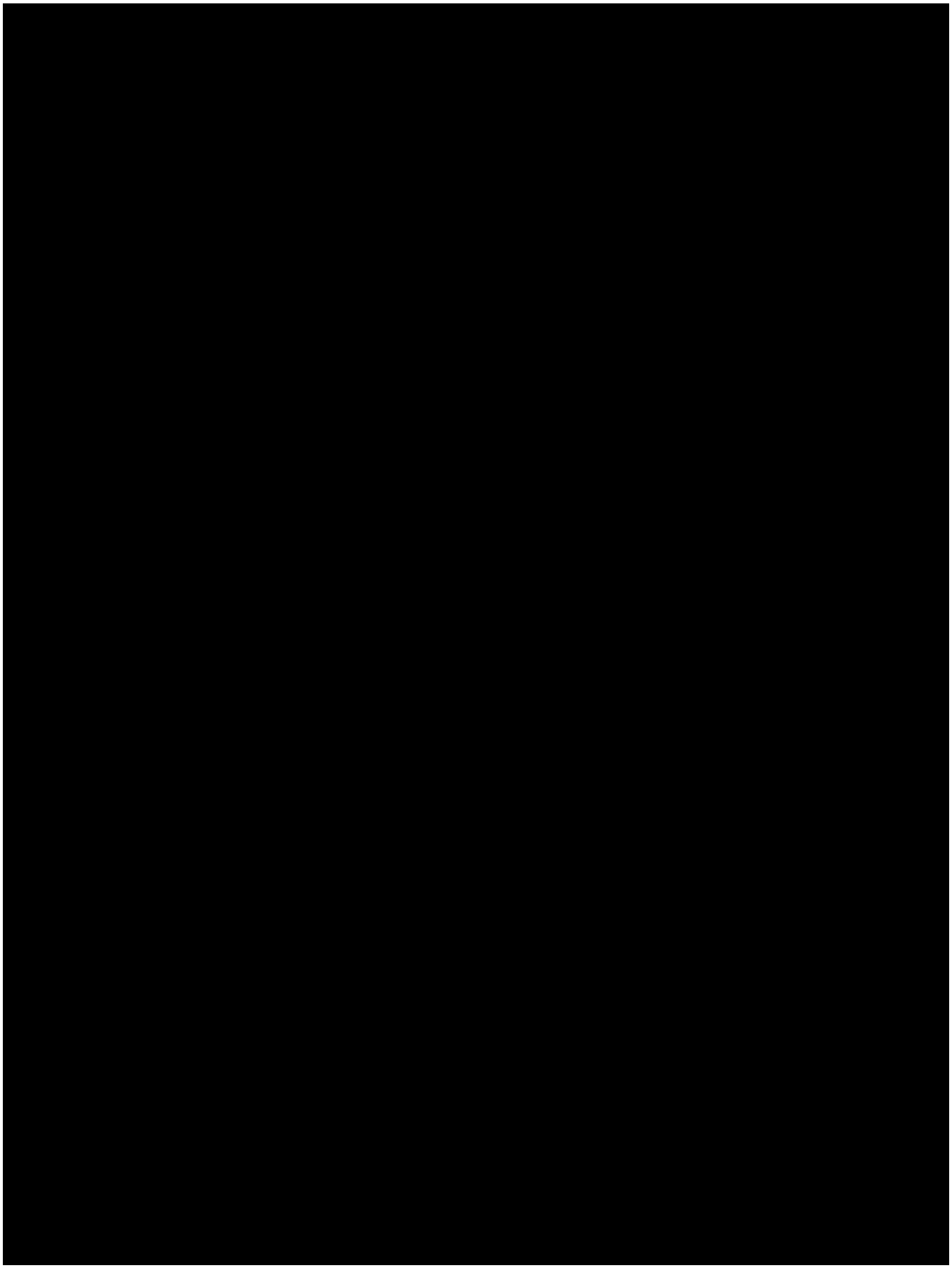
The above-mentioned national registers hold data on almost all inhabitants in Sweden (population 10.2 million) and Denmark (population 5.8 million). The coverage and quality of the Danish and Swedish Registers have been well established in the literature [21]. Due to the breadth of capture of clinical outcomes across providers as well as "cradle to grave" longitudinal coverage, these registries have been successfully utilized for numerous post-marketing safety studies.

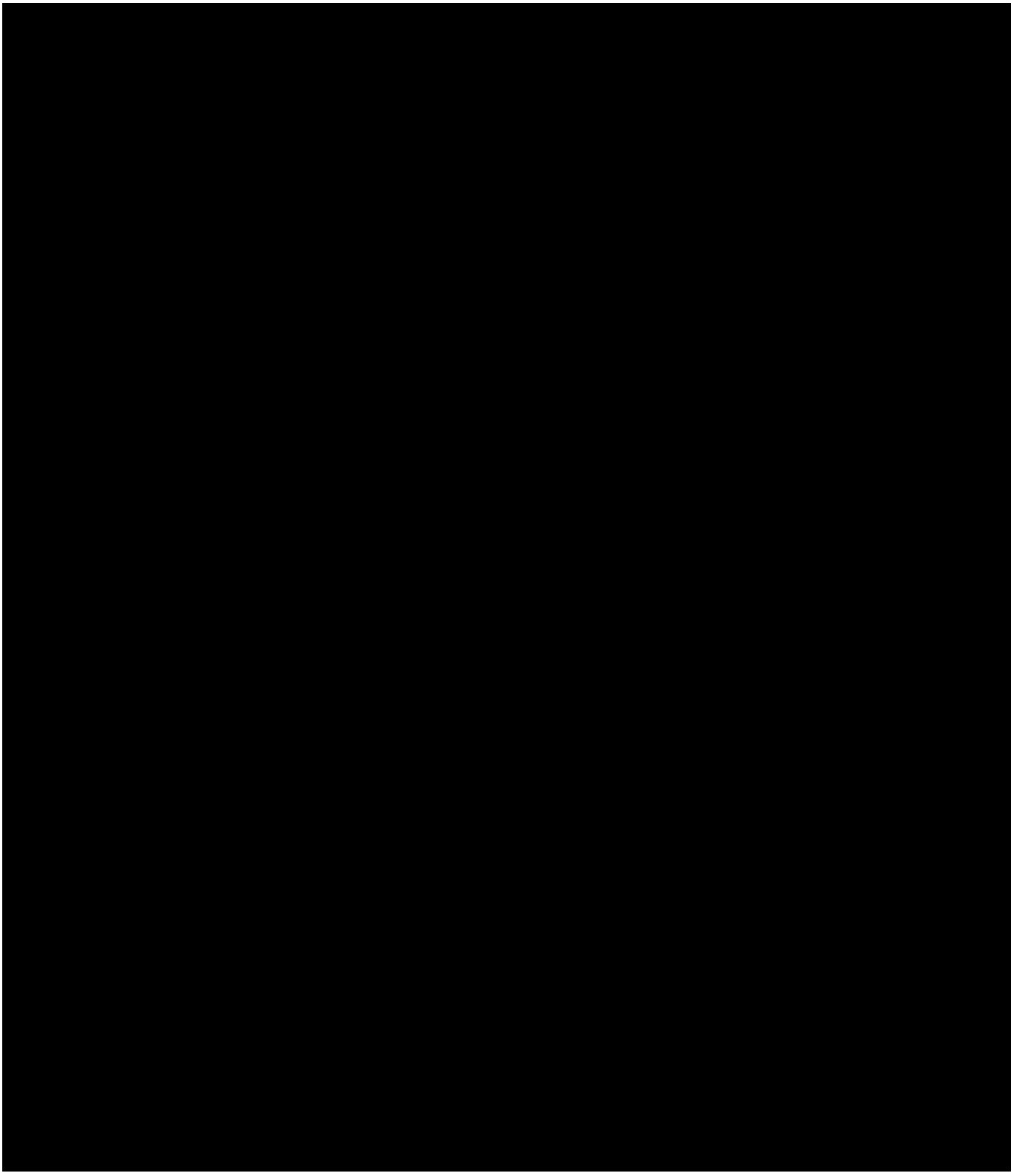
**Table 2 Data Sources in Denmark and Sweden**

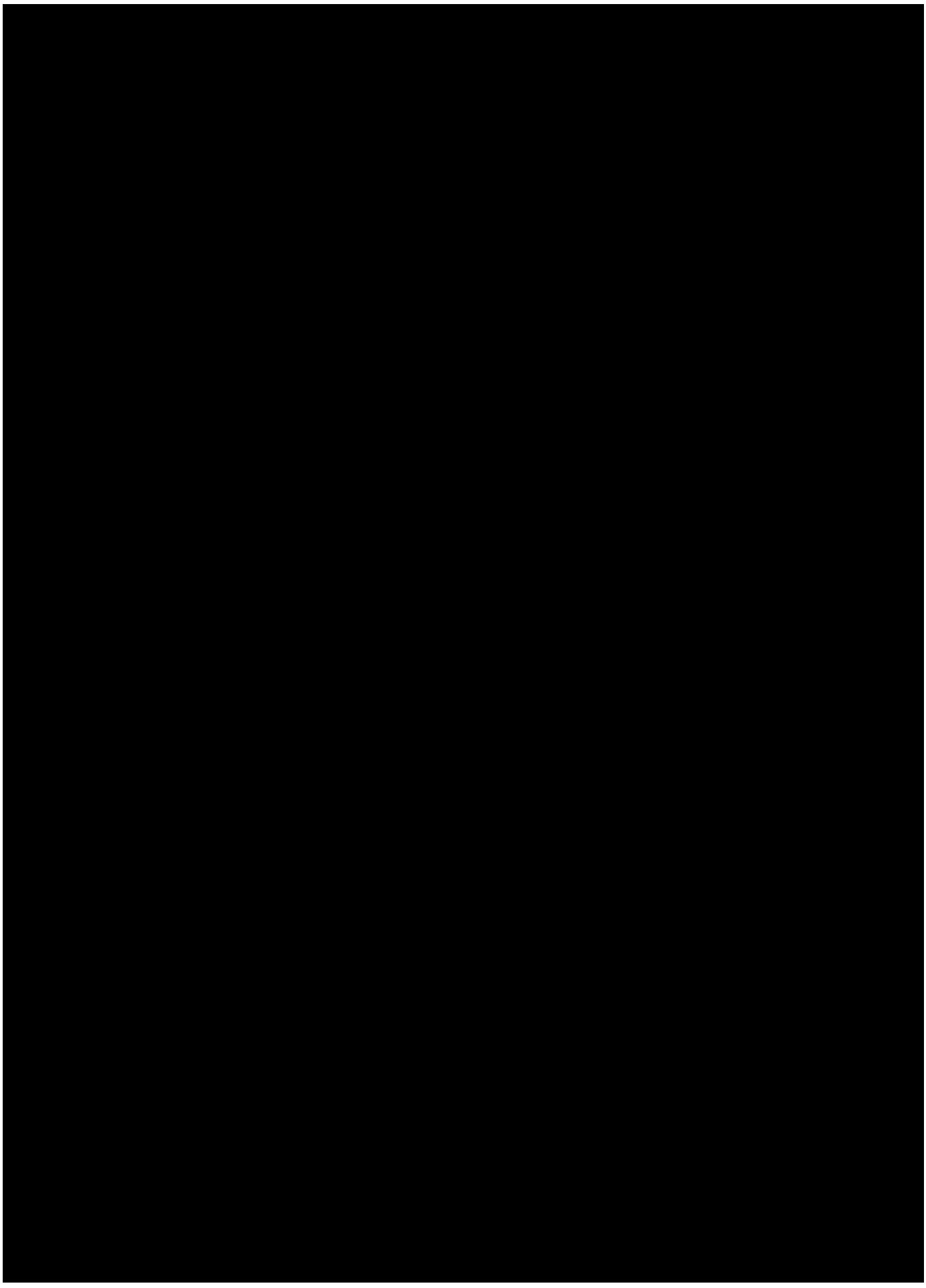
| **Sweden** | **Denmark** |
|---|---|
| | |
| | |
| | |
| | |
| | |
| | |
| | |

### *9.5. Study Size*









[redacted]

Since the potential available number of patients exposed to upadacitinib and comparators in the first five accrual years in the national registers in Denmark and Sweden is higher than the required target number of patients for the estimated sample size for the most important outcomes, these data sources are considered sufficient for this study.

The number of patients exposed to upadacitinib and other select systemic AD treatments will be monitored annually. If the number of upadacitinib users does not reach 50% of the target sample size by year 2024 (captured in the progress report in 2026), additional data sources will be considered to be added to the study.

### *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. The data holders in each country will create a unique dummy study identification number (SID) for each PIN. The coordinating investigator in each country will then receive the data where the PINs have been replaced by SIDs and these will be used for data linkage at the patient level. Therefore, the coordinating investigators in each country have access to pseudonymized data only.

In Sweden, data from the Swedish health registers will be provided by the Swedish National Board of Health and Welfare. Population data and socioeconomic data will be provided by Statistics Sweden. The pseudonymized individual-level data will be stored at a secure server at KI, and only members of the research team will have access to the data.

In Denmark, pseudonymized data from the Danish population, education, and health registers will be provided by Statistics Denmark. The register data will be accessed on-line via a password protected safe data portal.

Data will be cleaned and coded and harmonized analytic datasets will be prepared according to the specifications provided in the SAP. A 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. For cross-country pooled analyses, pseudonymized external data from the Swedish national health and population registers, will be provided by KI and uploaded at the safe data portal at Statistics Denmark, and members of the Swedish research team will have access to the data. Legal barriers towards transfer of individual data might be an issue, and if so meta-analyses of aggregated data will be performed instead of cross-country pooled analyses.

The statistical software packages STATA, R, and SAS will be used for data management and analyses.

### *9.7. Data Analysis*

The labeling updates due to the Article 20 procedure pose distinct challenges for the long-term safety study in atopic dermatitis (AD). First, patients treated with upadacitinib will be expected to differ from other select systemic treatments in baseline risk factors for major cardiovascular events (MACE), malignancy and/or venous thromboembolic events (VTE), based on the updated section 4.4 (Special warnings and precautions for use) of the RINVOQ Summary of Product Characteristics (SmPC). Second, high risk patients treated with upadacitinib will likely be those with "no suitable treatment alternatives" and be more likely to have failed other therapies, not responded to the lower dose of upadacitinib, and have higher disease burden. Third, the anticipated lower incidence of safety outcomes in low-risk patients raises feasibility concerns, particularly as these relate to precision requirements for comparative analyses.

To address these challenges, assessment of comparability of users of upadacitinib and other select systemic treatments for AD will be conducted through in-depth assessments of treatment pattern utilization and patient disposition at baseline (see Section 9.7.1).

#### 9.7.1. Descriptive Analysis

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

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

Drug utilization and individual baseline characteristics (e.g.; demographics, comorbidities, concomitant treatments, treatment experience, healthcare utilization)will be summarized for upadacitinib and select systemic AD treatments, separately for each country, by dose (upadacitinib), age group at initiation, relevant risk factors (e.g., malignancy, VTE, and MACE), and disease history as listed in the secondary objectives (moderate hepatic impairment, hepatitis B & C, severe renal impairment).

PS will be generated for upadacitinib users and other select systemic AD treatments users [55-57]. The distribution/overlap of propensity scores will be examined to assess the balance across cohorts. The SMD will be used to assess comparability across treatment groups if needed.

Person-years at risk and the number of safety outcomes for upadacitinib will be reported overall and across risk factor strata, crude incidence rates for upadacitinib will be presented. If suitable/comparable treatment cohorts can be identified, crude incidence rates for all safety outcomes will be provided for other select systemic AD treatments, as well.

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

### 9.7.2. Comparative Analysis

[redacted] analyses will be performed to compare upadacitinib and comparator treatments in the final report.

Comparisons of rates of safety outcomes between upadacitinib and comparator cohorts will be made with Cox proportional hazard regression models using appropriate strategies such as IPTW, PS matching/ stratification/ adjustments or others to achieve comparable balance across cohorts.

Table 7 below specifies the exposure definitions that will be used as time at risk for each outcome.

With the ITT exposure definition, individuals will be considered exposed to the first eligible treatment received until the end of follow-up while with the modified ITT individuals will be considered exposed to the first eligible treatment received and censored at treatment switching. With both ITT and modified ITT, Cox proportional hazards regression models with treatment group (upadacitinib, comparator) as exposure will be performed. For malignancy, exposure time and time to event will start to be counted from the lag-time (for main analysis 12 months) from index date.

With the time-varying exposure definition individuals may change exposure status when starting different treatments, and thus the treatment covariate is time-varying. Cox proportional hazards regression models with treatment group (upadacitinib, comparator, unexposed time, concomitant use/switch) as covariate will be performed. The time scale in the models will be time since start of the treatment group, i.e., time since beginning of the exposure to the specific treatment group (upadacitinib, comparator, unexposed time, concomitant use/switch).

The hazard ratio (HR) and 95% confidence interval (CI) will be reported from the Cox models. Kaplan-Meier curves for all outcomes will also be reported. In addition, 5-years overall survival rate will be presented for malignancy excluding NMSC, NMSC, MACE and all-cause mortality as well as 5-years event-free survival rates for malignancy excluding NMSC, NMSC and MACE.

Analyses will be performed based on pooled individual data, unless legal barriers towards transfer of individual data make it impossible, in which case meta-analyses of aggregated data will be performed instead. Methods for meta-analysis will be described in the SAP and the barriers for data pooling will be assessed in connection with the interim report.

**Table 7 Exposure definition per outcome**

| Outcome | Exposure definition |
|---|---|
| Malignancy (excluding NMSC), malignancy by type | [redacted] |
| NMSC | |
| MACE | |
| All-cause mortality | |
| VTE | |
| Serious (in-patient) infections (incl. opportunistic infections) | |
| HZ | |
| EH/KVE | |
| Active TB | |
| GI perforations | |
| DILI | |
| Fractures | |

#### *9.7.2.1. Sensitivity Analysis and Subgroup Analysis*

Sensitivity analyses for all safety outcomes will be performed among individuals in the study population with no prior use of any of the other systemic AD treatments within 12 months from *index date*. Sensitivity analyses with 0- and 6-months lag time for malignancy outcomes will be conducted.

In addition, subgroup analyses will be performed by upadacitinib dose, age group, relevant risk factors (e.g., malignancy, VTE, and MACE) and disease histories as listed in the secondary objectives.

Details on the sensitivity and subgroup analyses for all safety outcomes will be described in the SAP.

### 9.7.3. 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 institution's standard procedures. At a minimum, the statistical analysis will be supervised by a senior statistician and all study documents (protocol, report, publications) will be reviewed by the entire research team. A senior epidemiologist in each institution will review the report before submission to the sponsor. Clinical expertise is available for appropriate interpretation of results. 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 institution will also follow its internal quality control procedures and will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permission necessary to conduct this study.

## *9.9. Limitations of the Research Methods*

Some information is not collected in national registers including score-based AD disease severity and patient reported outcomes. Individuals only diagnosed with AD in primary care will not be included, and diagnostic information for conditions only seen in primary care will also be missing. The ability to assess and address bias will be detailed in the selection of comparison treatments and in the analytic approach. Confounders will be identified and adjusted for and the potential for residual confounding will be considered, and any relevant sensitivity analyses will be proposed. The role of unmeasured confounding and its influence on the study results will be discussed in the reports.

## *9.10. Other Aspects*

Not applicable.

# 10. Protection of Human Subjects

The study is based on register data only and will not require informed consent [58]. 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 pseudonymize the linked individual-level data by replacing the PIN with a project specific unique number. Country-specific data will be kept in secure servers at Statistics Denmark and at KI, and only members of the investigator teams will have access to the data in their respective countries. The investigators will comply with the EU General Data Protection Regulation (GDPR) and its implementation in the national legislations by May 2018 in the processing of personal data. Additionally, we will adhere to commonly accepted research practices, including those described in the following guidance documents: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, ENCePP Code of conduct, Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

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

## 11. Management and Reporting of Adverse Events/Adverse Reactions

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

## 12. Plans for Disseminating and Communicating Study Results

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

The study will be registered on ENCePP European Union electronic Register of Post-Authorization Studies (EU PAS Register) (http://www.encepp.eu/encepp_studies/indexRegister.shtml), within 30 calendar days after the study protocol is finalized and approved by the regulatory agency. The study protocol will be disclosed to the EU PAS Register within a target of 14 calendar days following the end of data collection. The study findings will be disclosed within 30 business days after the study report is finalized and shared with the regulatory agency.

The investigators may subsequently 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:** Cohort Study of Long-term Safety of Upadacitinib in the Treatment of Atopic Dermatitis in Denmark and Sweden |

| |
|---|
| **EU PAS Register® number:** EUPAS49230 (registration to be completed pending approval)<br>**Study reference number (if applicable):** N/A |

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Progress report(s) | ☒ | ☐ | ☐ | |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

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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) | ☒ | ☐ | ☐ | 9.2.1 |
| 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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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, 9.2 |
| 3.3 | Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 9.7 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☒ | ☐ | ☐ | 9.7 |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

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| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 9.2 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.2 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.2 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.1 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 9.2 |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.3 |
| 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? | ☐ | ☒ | ☐ | |
| 5.4 | Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.3 |
| 5.5 | Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☒ | ☐ | |
| 5.6 | Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 9.1 |

Comments:

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| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 8, 9.3 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3, Annex 3 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☒ | ☐ | |

Comments:

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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) | ☒ | ☐ | ☐ | 9.3, 9.7 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.9 |

Comments:

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

Comments:

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| **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 |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 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 |
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7, |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 9.7 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☒ | ☐ | |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 9.7 |

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

Comments:

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| **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:

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| **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:

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

Date: 19/Apr/2022

Signature: _____

## 16. Annex 3. Additional Information

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

**Table 3.1. Disease codes**

| ICD-10 Codes | Register | Description |
|---|---|---|
| **Atopic dermatitis** | | |
| [redacted] | Patient | |
| **Moderate hepatic impairment** | | |
| [redacted] | Patient | Sub-population for secondary objectives |
| **Chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV)** | | |
| [redacted] | | Sub-population for secondary objectives |
| **Severe renal impairment** | | |
| [redacted] | Patient | Sub-population for secondary objectives |

**Table 3.2. Treatment codes**

| Substance | ATC code/Procedure code Denmark (DK) only | DDD |
|---|---|---|
| Upadacitinib | [redacted] | 15 mg (oral) |
| **Systemic comparator treatments** | | |
| Azathioprine | [redacted] | 0.15 g (oral and parenteral) |
| Ciclosporin | [redacted] | 25 mg (oral and parenteral) |
| Dupilumab | [redacted] | 21.4 mg (parenteral) |
| Methotrexate | [redacted] | 2.5 mg (oral and parenteral) |
| Mycophenolate mofetil | [redacted] | 2 g (oral and parenteral) |

**Table 3.3. Outcomes**

| Diagnosis Codes (ICD-O-3 and ICD-10) | Register | History exclusion look-back period | Description |
|---|---|---|---|
| **Malignancies excluding NMSC** | | | |
| [redacted] | Cancer/Patient | 5 years | |
| **Non-melanoma skin cancer (NMSC)** | | | |
| [redacted] | Cancer/Patient | 5 years | |
| **MACE (non-fatal MI, non-fatal stroke, CV death)** | | | |
| [redacted] | Patient, Cause of Death | | |
| **Serious infections (any hospital-treated infections, including opportunistic infections)** | | | |
| [redacted] | Patient | 1 year | Respiratory tract infections.<br>In-patient only |
| [redacted] | Patient | | Infections of the gastrointestinal tract*<br>In-patient only |
| [redacted] | Patient | | Urinary tract infection |
| [redacted] | Patient | | Infections of the skin and subcutaneous tissue<br>In-patient only |
| [redacted] | Patient | | Other infections<br>In-patient only |
| **Venous thromboembolic event (VTE)** | | | |
| [redacted] | Patient | 5 years | |
| **Herpes zoster (HZ)** | | | |
| [redacted] | Patient | 1 year | |
| **Eczema herpeticum (EH)/Kaposi's varicelliform eruption (KVE)** | | | |
| [redacted] | Patient | 1 years | |
| **Active tuberculosis (TB)** | | | |

| Diagnosis Codes (ICD-O-3 and ICD-10) | Register | History exclusion look-back period | Description |
|---|---|---|---|
| [redacted] | Patient | 5 years | J04AK05 (bedaquiline)J04AK01 (pyrazinamide)J04AK02 (ethambutol) |
| **Gastrointestinal (GI) perforations** | | | |
| [redacted] | Patient | 5 years | |
| **Drug-induced liver injury (DILI)** | | | |
| [redacted] | Patient | 5 years | Toxic liver disease |
| **All-cause mortality** | | | |
| [redacted] | Cause of Death | | All deaths in Cause of Death Register |
| **Fractures** | | | |
| [redacted] | Patient | 5 years | |