**Janssen-Cilag International**

**Non-interventional Postauthorization Safety Study - Protocol**

# An Observational Longitudinal Post-authorization Safety Study of STELARA® in the Treatment of Psoriasis and Psoriatic Arthritis: Analysis of Major Adverse Cardiovascular Events (MACE) using Swedish National Health Registers

**Short title**
**Quantify STELARA MACE Study**

**Protocol PCSIMM004697**

**STELARA® (Ustekinumab)**

**EU PAS Register Number:** Study Not Registered

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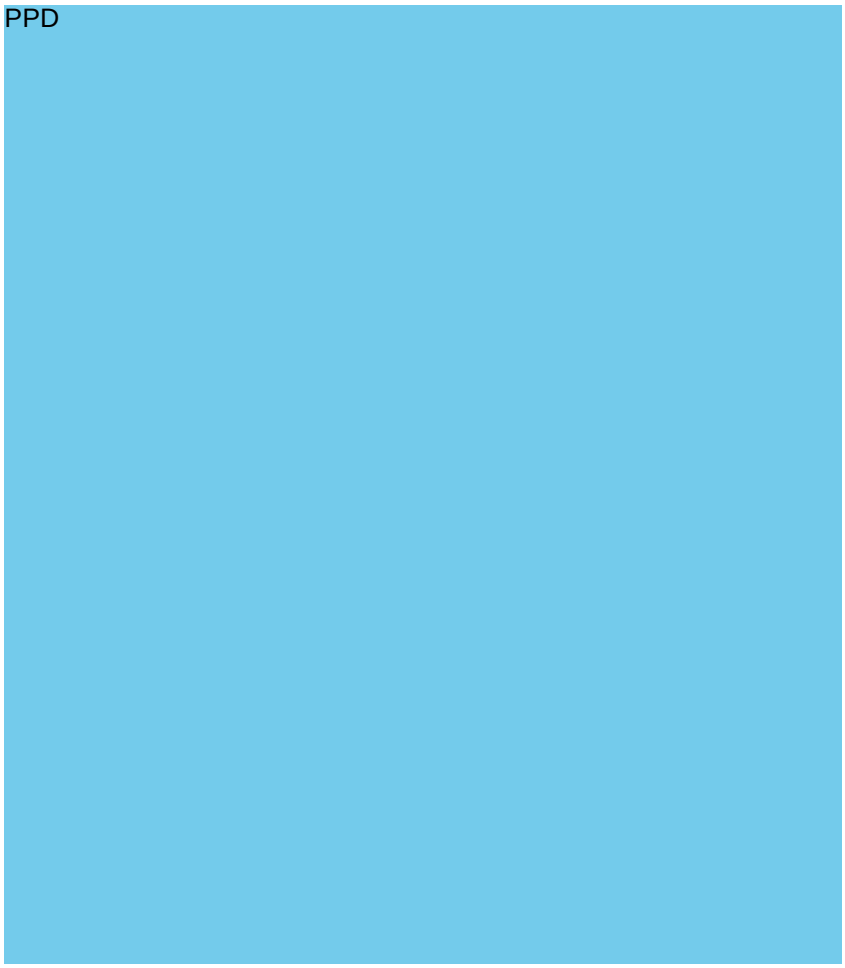
|---|---|---|---|
| **Status:** | Approved | | |
| **Protocol version:** | 3.0 | **Version date:** | 26 October 2022 |
| **Prepared by:** | Janssen Cilag International N.V. | | |
| **EDMS number:** | EDMS-RIM-622563, 4.0 | | |

**Compliance:** This study will be conducted in compliance with the protocol and applicable regulatory requirements.

# 1. PASS INFORMATION

| | |
|---|---|
| Title: | **An Observational Longitudinal Post-authorization Safety Study of STELARA® in the Treatment of Psoriasis and Psoriatic Arthritis: Analysis of Major Adverse Cardiovascular Events (MACE) using Swedish National Health Registers** |
| Protocol version: | 3.0 |
| Date of last version of the protocol: | 21 January 2022 |
| EU PAS Register No: | Study not registered |
| Active substance (INN common name): | Ustekinumab |
| Pharmaco-therapeutic group (ATC Code): | L04AC05 |
| Medicinal product(s): | STELARA® (ustekinumab) |
| Product reference: | EU/1/08/494 |
| Procedure number: | EMEA/H/C/000958 |
| Name of Marketing Authorization Holder(s) | Janssen-Cilag International NV |
| Joint PASS | No |
| Research question and objectives | The primary objective of the study is to estimate and compare the risk of major adverse cardiovascular events in psoriasis and psoriatic arthritis patients initiating treatment with ustekinumab relative to patients initiating treatment with etanercept in routine clinical practice in Sweden.<br><br>The secondary objectives are to estimate and compare the risk of major adverse cardiovascular events in psoriasis and psoriatic arthritis patients initiating treatment in routine clinical practice in Sweden with:<br>• ustekinumab relative to patients initiating treatment with adalimumab;<br>• ustekinumab relative to patients initiating treatment with secukinumab;<br>• adalimumab relative to patients initiating treatment with etanercept;<br>• secukinumab relative to patients initiating treatment with etanercept. |
| Country(-ies) of study | Sweden |
| Authors | PPD |


PPD

## 2. MARKETING AUTHORIZATION HOLDER(S)

| | |
|---|---|
| Name of Marketing Authorization Holder: | Janssen-Cilag International NV |
| Address: | Turnhoutseweg 30<br>B-2340 Beerse<br>Belgium |
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Qualified Person Pharmacovigilance:

| | |
|---|---|
| Name: | Dr. Laurence Oster-Gozet, PharmD, PhD |
| Signature: | electronic signature appended at the end of the protocol |
| Date: | |

## 3. RESPONSIBLE PARTIES

| | |
|---|---|
| Coordinating Investigator | Jonas Banefelt, MSc. |
| Contact person for this protocol: | PPD |
| E-mail address or telephone number of contact person: | PPD |

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## ADDITIONAL INFORMATION PROVIDED IN ANNEX 1



## LIST OF IN-TEXT TABLES AND FIGURES

### TABLES

## AMENDMENTS AND UPDATES

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and will follow the review and approval process in accordance with local regulations.

There are no amendments for this protocol.

# 4. ABSTRACT

**Protocol Title: An Observational Longitudinal Post-authorization Safety Study of STELARA® in the Treatment of Psoriasis and Psoriatic Arthritis: Analysis of Major Adverse Cardiovascular Events (MACE) using Swedish National Health Registers** (3.0, 26 October 2022)

**Sponsor's Responsible Medical Officer:** PPD

NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

**Background and Rationale**

STELARA (ustekinumab) is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23, indicated for the treatment of plaque psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease, and ulcerative colitis.

Following the assessment of the ustekinumab Periodic Safety Update Report (PSUR) procedure covering the interval from 01 January 2020 to 31 December 2020 (EMEA/H/C/PSUSA/00003085/202012) the EMA/PRAC requested to include 2 additional post-authorization safety studies (PASS's) in the EU-Risk Management Plan to expand the evidence base on the risk of major adverse cardiovascular events (MACE) associated with ustekinumab in patients with PsO and PsA.

The purpose of this study is to aid in addressing the risk of MACE in PsO and PsA patients treated with ustekinumab.

**Research Question and Objectives**

This study will estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with STELARA (ustekinumab) relative to patients initiating treatment with etanercept, adalimumab, and secukinumab in routine clinical practice in Sweden.

The primary objective is to estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with ustekinumab (L04AC05) relative to patients initiating treatment with etanercept in routine clinical practice in Sweden.

The secondary objectives are to:

- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with ustekinumab relative to patients initiating treatment with adalimumab in routine clinical practice in Sweden
- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with ustekinumab relative to patients initiating treatment with secukinumab in routine clinical practice in Sweden
- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with adalimumab relative to patients initiating treatment with etanercept in routine clinical practice in Sweden
- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with secukinumab relative to patients initiating treatment with etanercept in routine clinical practice in Sweden

The outcomes of interest are:

- MACE (composite outcome of myocardial infarction, ischemic stroke, and cardiovascular death), as measured by:

  Stabilized propensity score-weighted hazard ratios (primary endpoint)

  Cumulative incidence, unadjusted (secondary endpoint)

  Incidence rates, unadjusted (secondary endpoint)

  - Incidence rates will also be estimated for each component of MACE

**Study Design**

This is a non-interventional database study based on secondary use of data. This observational cohort study with an active-comparator, new-user design, will use patient-level data from Swedish population-based national registers. The risk of MACE will be estimated for PsO and PsA patients initiating treatment with ustekinumab and compared to the risk of MACE in PsO and PsA patients initiating treatment with other biologics of interest (etanercept, adalimumab, secukinumab) in routine clinical practice in Sweden.

Patients will be allocated to mutually exclusive incident user cohorts based on the first study drug initiated during the study inclusion period. The ustekinumab cohort will consist of patients initiating ustekinumab as the first study drug during the study inclusion period, the etanercept cohort will consist of patients initiating etanercept as the first study drug during the study inclusion period, etc. The ustekinumab cohort will be compared to each respective cohort of etanercept (primary objective), adalimumab, and secukinumab (secondary objectives) incident users. To further contextualize the results from the ustekinumab comparisons, the adalimumab and secukinumab cohorts will also be compared to the etanercept cohort.

The new-user treatment cohorts will be analyzed in the context of two populations: 1) the bio-naïve population and 2) the overall incident user population. The bio-naïve population will only include patients initiating a treatment with a cohort-defining biologic who have not been previously treated with any biologic, based on all available dispensation data. The overall incident user population will include patients initiating treatment with a cohort-defining biologic who may or may not have previously been treated with another biologic. The main analysis will compare ustekinumab to etanercept, adalimumab and secukinumab bio-naïve populations using an intention-to-treat (ITT) definition of exposure time (time at risk), in which patients who discontinue the index biologic will continue to be followed based on their index treatment. Additional analyses of the treatment cohorts will analyze the overall incident user population using an ITT definition of exposure time, and both bio-naïve and overall incident user populations using an as-treated definition of exposure time.

Risk of MACE will be analyzed using cumulative incidence estimation and incidence rates for unadjusted risk, estimated for each treatment cohort. A Cox proportional hazards (time-to-event) regression model with stabilized inverse probability of treatment weighting by propensity scores will be used to adjust for measured confounding due to treatment selection. As such the following endpoints will be reported for each treatment cohort (for both populations of interest, reported separately), using both an ITT and an as-treated exposure definition: 1) cumulative incidence (estimated probability) of MACE within 6, 12, 24, 36, 48, 60, and 72 months of index date, and beyond if possible, together with cumulative incidence curves over the entire available follow-up (secondary endpoint); 2) incidence rates of MACE and each respective component of MACE during follow-up (secondary endpoint); and 3) propensity score weighted hazard ratios of MACE for ustekinumab use compared to use of each of the respective other biologics of interest (primary endpoint) as well as for adalimumab and secukinumab use compared to etanercept.

**Setting and Patient Population**

This is a non-interventional database study based on secondary use of patient-level data from Swedish population-based national registers. The study population of interest is adult PsO and PsA patients diagnosed in secondary care initiating treatment with ustekinumab or another biologic of interest (i.e., etanercept, adalimumab, secukinumab) during the study inclusion period. The study inclusion period is defined as 1 July 2009 to 30 December 2021. Patients will be included if they have a PsO/PsA primary diagnosis anytime from 1 January 2001 to 30 December 2021, and have initiated treatment (first ever dispensation in the data) with one of the study drugs during the study inclusion period. As such, patients cannot be included in a specific treatment cohort if they have been treated with that drug prior to the start of the study inclusion period. First ever dispensation of any of the study drugs occurring before the first diagnosis of PsO/PsA will also exclude the patient from inclusion into that specific study drug cohort.

In the primary analysis, an ITT exposure definition will be used. As such, patients will be followed from first initiation of treatment with a study drug during the study inclusion period until MACE, death, emigration, or end of data availability, whichever comes first. In the secondary analysis, an as-treated exposure definition will be used; patients will thus be followed from first initiation of treatment with a study drug during the study inclusion period until MACE, death, switch to another biologic, discontinuation of the cohort-defining biologic, emigration, or end of data availability, whichever comes first.

The end of the study period corresponds to the registry data extraction date (31 December 2021) for all patients except for patients registered in region PPD at index date. Due to a procurement agreement with the PPD regional council, ustekinumab has been administered at hospitals instead of dispensed at pharmacies in PPD from 2016 and onwards. Data on hospital-administered medications is not fully captured in the register data to be used and therefore there will be incomplete data on ustekinumab use in PPD in the database. For patients living in PPD, the inclusion period will thus run from 1 July 2009 to 30 December 2015. Similarly, in the secondary analysis in which an as-treated exposure definition will be used, these patients will be censored on 31 December 2015, instead of 31 December 2021. Note that while the follow-up period will end on 31 December 2021, the inclusion period ends on 30 December 2021 as the data resolution is on the date-level, meaning patients will need to be included prior to 31 December 2021 in order to be included in the planned time-to-event analyses. In addition, access to data covering 2020-2021 is contingent on timely delivery from the register holder, which is not guaranteed due to the possibility of delays related to the ongoing COVID-19 pandemic.

**Variables**

The key variables included in this study are summarized in the table below (next page).

The primary outcome of interest is incident MACE, defined as any of cardiovascular death, ischemic stroke, and/or myocardial infarction.

**Variable overview and summary table**

| **Study population defining variables** | **Definition** |
|---|---|
| Psoriasis diagnosis | ICD-10: L40.0-4, L40.8-9 |
| Psoriatic arthritis diagnosis | ICD-10: L40.5, M07.0-3 |
| **Exposure(s)** | |
| Ustekinumab | ATC: L04AC05 |
| Adalimumab | ATC: L04AB04 |
| Etanercept | ATC: L04AB01 |
| Secukinumab | ATC: L04AC10 |
| **Outcomes(s)** | |
| Myocardial infarction | ICD-10: I21 |
| Ischemic stroke | ICD-10: I63-I64 |
| CV death | Codes for underlying cause of death in the Cause of Death Register, based on ICD-10 I chapter |
| **Covariates** | |
| Age | Age in years at index date |
| Sex | Male/Female at index date |
| Region of residence | Living county at index date |
| Time since disease onset | Time since disease onset in years |
| Index year | Calendar year at index |
| Education level | Highest education level attained the year closest to index date |
| Marital status | Married or Registered Partnership at the observational time closest to index date |
| Biologic/JAK-inhibitor experience | ATC: L04AA24, L04AA29, L04AA44, L04AB01, L04AB02, L04AB04, L04AB05, L04AB06, L04AC10, L04AC12, L04AC13, L04AC16, L04AC17, L04AC18 |
| Biologic/JAK-inhibitor treatment line | |
| TNF inhibitor experience | ATC: L04AB04, L04AB05, L04AB01, L04AB06, L04AB02 |
| IL inhibitor experience | ATC: L04AC12, L04AC16, L04AC13, L04AC18, L04AC10, L04AC17, L04AC05 |
| JAK-inhibitor experience | ATC: L04AA44, L04AC05 |
| The sum of the number of inpatient stays and outpatient visits for PsO or PsA (proxy for disease severity) | ICD-10: L40.0-5, L40.8-9, M07.0-3 |
| Charlson comorbidity index | ICD-10 codes; during the five years prior to and including index date |
| Antihypertensive drug use | ATC: C02, C03, C07-09; drugs during the year (365 days) prior to and including index date |
| Nicotine replacement therapy | ATC: N07BA; dispensations during the year prior to and including index date |
| Non-steroidal anti-inflammatory drug (NSAID) use | ATC: M01A; dispensations during the year prior to and including index date |
| Presence of Crohn's disease | ICD-10: K50; during the five years prior to and including index date |
| Presence of ulcerative colitis | ICD-10: K51; during the five years prior to and including index date |
| Presence of uveitis | ICD-10: H20; during the five years prior to and including index date |
| Presence of diabetes mellitus | ICD-10: E10-E14; during the five years prior to and including index date |
| History of obesity | At least one of the following:<br>• Obesity, ICD-10: E66; during the five years prior to and including index date<br>• Bariatric surgery, Klassifikation av vårdåtgärder (Swedish medical procedures) codes: JDF; during the five years prior to and including index date |
| Chronic obstructive pulmonary disease | ICD-10: J41-J44; during the five years prior to and including index date |
| COVID-19 | ICD-10: U07; during the five years prior to and including index date |

| | |
|---|---|
| Documented cardiac or systemic atherosclerotic vascular disease (peripheral arterial disease, coronary artery disease, cerebrovascular disease, past revascularization procedures) | At least one of the following:<br>• Peripheral arterial disease, ICD-10: I70.0, I70.2, I73.9; during the five years prior to and including index date<br>• Coronary artery disease, ICD-10: I20-I25; during the five years prior to and including index date<br>• Cerebrovascular disease, ICD-10: per Charlson comorbidity index; during the five years prior to and including index date<br>• Revascularizations, Klassifikation av vårdåtgärder (Swedish medical procedures) codes FNA, FNB, FNC, FND, FNE, FNF, FNG, FNW: during the five years prior to and including index date |
| Dyslipidemia | At least one of the following:<br>• Use of hypolipidemic agents, ATC: C10AA, C10AB, C10AX, C10B; dispensations during the year prior to – and including – index<br>• Presence of disorders of lipoprotein metabolism and other lipidaemias, ICD-10: E78; during the five years prior to – and including index date |
| History of MACE | ICD-10: I21, I63-I64; during the five years prior to and including index date |
| Use of non-biologic immunomodulators | Methotrexate, cyclosporine, mycophenolate, apremilast, fumaric acid, oral retinoids, oral glucocorticoids, sulfasalazine, leflunomide, or oral tacrolimus dispensation dispensations during the year prior to and including index date |
| Use of phototherapy | Klassifikation av vårdåtgärder (Swedish medical procedures) codes DQ012, DQ013, DQ014,<br>DQ016 during the year prior to and including index date |

## Data Sources

The data sources for the study are Swedish national population-based registers. Data for all patients with a PsO and/or PsA diagnosis recorded between 1 January 2001 and 30 December 2021 in specialist care in Sweden will be extracted from registers held by the Swedish National Board of Health and Welfare (NBHW) (see table below). All data are pseudonymized and will be submitted to the investigator with study specific subject-ids for linkage between datasets.

**Summary of key data sources used in the study**

| Type of Data | Source Registry | Details |
|---|---|---|
| Inpatient care | National Patient Registry (NPR) | Includes the dates and associated diagnoses for all inpatient specialist care in Sweden, as well as demographics such as patient age and sex. Data are available from 1964 and onwards. |
| Outpatient specialist care | National Patient Registry (NPR) | Includes the dates and associated diagnoses with all outpatient specialist care in Sweden, as well as demographics such as patient age and sex. Data are available from 2001 and onwards. |
| Prescriptions | Prescribed Drug Registry (PDR) | All prescriptions dispensed by patients at Swedish pharmacies are included in this registry. The data includes date of prescription and dispensation, formulation, amount dispensed, defined daily dose (DDD), and others from July 2005 and onwards. |
| Mortality | Cause of Death Registry (CDR) | Includes the cause and date of all deaths in Sweden, from 1952 and onwards. |

### Study Size

The projected number of patients to be analyzed in the primary objective, comparing ustekinumab to etanercept, using the primary analysis definitions is ~580 bio-naïve ustekinumab initiators and ~5400 bio-naïve etanercept initiators. These projections are based on the number of bio-naïve ustekinumab and etanercept initiators observed in a similar analysis based on the same underlying register data, covering data until and including 2019 (investigator data on file). Further, publicly available data from the Swedish National Board of Health and Welfare on the total number of patients with dispensations for the study drugs of interest (all indications) between 2009 and 2020 (see table below) have informed 1) the expected amount of follow-up for each treatment cohort, 2) the assumption that the adalimumab and etanercept cohorts are approximately equal in size, and 3) the number of additional patients to be included based on the addition of data from 2020 and 2021.

**Number of patients with dispensations of study drugs, 2009-2020**

| Treatment | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adalimumab | 5427 | 6368 | 7093 | 7775 | 8487 | 9239 | 10161 | 10860 | 11530 | 12592 | 18236 | 13494 |
| Etanercept | 7315 | 7744 | 7841 | 7845 | 8162 | 8786 | 9298 | 10758 | 12561 | 14500 | 14086 | 22285 |
| Ustekinumab | 14 | 74 | 161 | 221 | 322 | 516 | 759 | 808 | 1044 | 1362 | 1705 | 2079 |
| Secukinumab | 0 | 0 | 0 | 0 | 0 | 0 | 103 | 873 | 1495 | 1857 | 2011 | 2194 |

*Source: The statistics database of the Swedish National Board of Health and Welfare*[a]

The background rate for MACE has been estimated to ~9.5 per 1000 patient-years in populations of patients using etanercept for PsO/PsA[b]. Assuming the same background rate, a non-time-dependent risk of events, a ratio of ustekinumab and etanercept subjects of 580:5400 with a mean follow-up of 3 and 4 years, respectively, and using a type I error rate of 0.05, the smallest effect size that can be detected with a preserved power of 80% would correspond to a hazard ratio of 1.9, based on the method described by Schoenfeld[c].

### Data Analysis

Patient characteristics covering demographic and clinical characteristics, comorbidities, co-medication use, and cardiovascular risk factors will be reported for each treatment cohort in the overall incident user population and in the bio-naïve population.

The primary outcome of MACE will be analyzed using time-to-event methodology. Cumulative incidence and incidence rates of MACE together with total amount of available follow-up will be reported for each treatment cohort. Cox proportional hazards regression with stabilized inverse probability of treatment weighting by propensity scores will be used to adjust for confounding by treatment selection. The propensity score will be calculated as the predicted probability of initiating the exposure of interest (i.e., ustekinumab in the primary objective) using multivariable logistic regression conditional on baseline covariates that are potential confounders and those prognostic of outcome but not associated with treatment. This weighting strategy estimates the average treatment effect.

The following endpoints will be reported for each treatment cohort (for bio-naïve and overall incident user population reported separately), using both an ITT and an as-treated exposure definition: 1) cumulative incidence (probability) of MACE within 6, 12, 24, 36, 48, and 60, 72 months of index date, and beyond if possible, together with cumulative incidence curves over the entire available follow-up; 2) incidence rates

[a] National Board of Health and Welfare (NBHW), Socialstyrelsens statistikdatabas för läkemedel.

[b] Reich, K., U. Mrowietz, M. Radtke, et al., Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. Archives of dermatological research, 2015. 307(10): p. 875 883.

[c] Schoenfeld, D.A., Sample size formula for the proportional hazards regression model. Biometrics, 1983: p. 499 503.

of MACE during follow-up; and 3) weighted hazard ratios of MACE for ustekinumab use compared to use of each of the respective other biologics of interest.

The primary comparison will be between bio-naïve patients starting ustekinumab and bio-naïve patients starting etanercept using an ITT exposure definition.

To test the robustness of the results to e.g. alternate specifications of the outcome and exposure period, the following sensitivity analyses will be performed:

1. Expanding the definition of MACE to also include unstable angina (I20.0), reinfarction (I22), and transient ischemic attacks (G45)
2. Utilizing the ITT definition of time at risk, but following patients for a maximum of two years (730 days) after switch and/or discontinuation of study drug, to ensure reasonable temporal proximity between events and the exposure to which events are attributed
3. Changing the end of study date from 31 December 2021 to 31 December 2019, to ensure that any potential impact of the COVID-19 pandemic on e.g. dispensation patterns or data collection does not alter study findings

**Milestones**

| **Milestone** | **Due date** |
|---|---|
| Start of data collection | 1 July 2009 |
| End of data collection | 31 December 2021 |
| Submission of protocol | 26 January 2022 |
| Protocol approval | 28 February 2023 |
| Final report of study results | 30 June 2023 (4 months after protocol approval by EMA) |

## 5. MILESTONES

The initial due dates for key milestones in this study are outlined below.

| **Milestone:** | **Due Date:** |
|---|---|
| Start of data collection | 1 July 2009 |
| End of data collection | 31 December 2021 |
| Submission of protocol | 26 January 2022 |
| Protocol approval | 28 February 2023 |
| Final report of study results | 30 June 2023 (4 months after protocol approval by EMA) |

# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

## Abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical Classification |
| CAT | Categorical |
| CDR | Cause of Death Registry |
| CON | Continuous |
| CV | Cardiovascular |
| DDD | Defined Daily Dose |
| FOIA | Freedom of Information Act |
| GDPR | General Data Protection Regulation |
| GPP | Good Pharmacoepidemiology Practices |
| HR | Hazard Ratio |
| ICD-10 | International Classification of Diseases, 10$^{th}$ revision |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IL | Interleukin |
| IPTW | Inverse probability of treatment weighting |
| IRB | Institutional Review Board |
| ISPE | International Society for Pharmacoepidemiology |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| ITT | Intention-to-treat |
| JAK | Janus Kinase |
| LDL-C | Low-Density Lipoprotein Cholestrol |
| MACE | Major Adverse Cardiovascular Events |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| NBHW | National Board of Health and Welfare |
| NPR | National Patient Registry |
| NSAID | Non-steroidal anti-inflammatory drug |
| PDR | Prescribed Drug Registry |
| PQC | Product Quality Complaint |
| PRO | Patient-reported outcome(s) |
| PsA | Psoriatic Arthritis |
| PsO | Psoriasis |
| RMP | Risk Management Plan |
| SD | Standard Deviation |
| SSN | Social Security Number |
| TNF | Tumor Necrosis Factor |
| UA | Unstable Angina |

**Definition of Term(s)**

| | |
|---|---|
| As-treated exposure definition | In analyses utilizing the as-treated exposure definition, exposure time will be measured from first initiation of treatment with a study drug during the study inclusion period until an event (MACE), (non-CV) death, switch to another biologic, discontinuation of the cohort-defining biologic, emigration, end of data availability, or 31 Dec 2015 for patients living in PPD at the index date. In the case of a switch to another biologic, the exposure time of the cohort-defining study drug will end on the date of dispensation of the biologic the patient switches to. |
| Bio-naïve | A patient will be considered bio-naïve and included in the bio-naïve cohort if that patient has no dispensations of a biologic or Janus kinase inhibitor indicated for psoriasis and/or psoriatic arthritis prior to index date in the available data. |
| Discontinuation of index treatment | Discontinuation of treatment is not registered explicitly in the data but must be inferred by absence of recurrent dosing (or dispensing) after a clinically expected interval. Patients will be considered to have discontinued a cohort-defining drug after the inferred end of a previous dispensation's dispensation interval if 90 days pass with no new dispensation of said drug following the inferred end. The inferred length of each dispensation will be based on the amount dispensed and recommended maintenance dosing intervals for the respective treatment. |
| Incident user | A patient with a first ever (in the available data) dispensation of a cohort-defining treatment during the study inclusion period. |
| Index date | The index date is designated as the date of first dispensation of the index treatment during the study inclusion period for patients meeting the study selection criteria. |
| Index treatment | Index treatment is assigned during the study period based on the first cohort-defining treatment after study start. |
| Intention-to-treat exposure definition | In analyses utilizing the intention-to-treat exposure definition, exposure time will be measured from first initiation of treatment with a study drug during the study inclusion period until an event (MACE), (non-CV) death, emigration, or end of data availability, whichever comes first. |
| Post Authorization Safety Study (PASS) | Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. |
| Registry | An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. |
| Retrospective non-interventional study | A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information from the patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information. |
| Study | The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any interventional treatments or procedures, planned or otherwise, have been provided or performed. |

# 6. BACKGROUND AND RATIONALE

## 6.1. Background

Psoriasis (PsO) is a common, chronic immune-mediated inflammatory disease which is characterized by rapid skin growth leading to patches of abnormal skin and/or skin lesions which cause itching and pain. The extent of psoriatic skin change varies, from small areas to complete body coverage. Although there are great individual variations, the burden of PsO can be immense, psychosocially, emotionally, and physically. It has been estimated that at least 100 million people are affected worldwide. In Sweden, the prevalence of PsO is 2-3%, corresponding to approximately 250,000 to 300,000 people affected [1 4].

Psoriatic arthritis (PsA) is a chronic, inflammatory disease that is manifested as pain, stiffness, and swelling in and around the joints or/and in the back [5]. PsA can show different additional manifestations outside the joints and the disease can cause irreversible structural damage on the affected joints when untreated. The prevalence of PsA is lower than that of PsO, estimated at between 0.1% and 0.42% in the general population, or between 7% and 31% in people with PsO [5, 6]. As with PsO, PsA imposes a large quality of life and cost burden on affected patients [7]. Studies have estimated costs incurred by PsA patients to be twice that of patients with PsO alone [5]. Similarly, patients with PsA have been shown to have poorer quality of life than patients with PsO alone [8, 9].

There is no cure for PsO or PsA, but a range of disease managing treatments exists, including: topical agents for mild disease; phototherapy and conventional systemic treatments including methotrexate and apremilast; and biologic therapies for more severe cases. Biologic treatments such as tumor necrosis factor (TNF) inhibitors etanercept, adalimumab, infliximab, certolizumab pegol and golimumab, as well as interleukin (IL)-12/IL23 and IL17 and IL23 p19 inhibitors, including STELARA (ustekinumab), brodalumab, secukinumab, ixekizumab and guselkumab, are recommended in moderate to severe PsO and PsA in Sweden, or in patients who have not responded to or are intolerant to other systemic treatments [10].

STELARA (ustekinumab) is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of the human cytokines IL-12 and IL-23, indicated for the treatment of plaque PsO, PsA, Crohn's disease, and ulcerative colitis.

Results from clinical studies on approved IL12/23 inhibitors, as well as of TNF inhibitors, have demonstrated that these therapies are generally not associated with an increased risk of adverse cardiovascular (CV) outcomes. This has been further demonstrated in real-world safety surveillance studies of these therapies. While a possible association with major adverse CV events (MACE) was noted in the Phase 2 ustekinumab PsO trial, this was not observed in Phase 3 trials, including long-term follow-up. Nonetheless, given the numeric imbalance observed in the Phase 2 trial and the known increased risk of CV events in the PsO and PsA populations, especially in patients with severe disease [11 14], CV events are listed as an important potential risk in the risk management plan (RMP) for ustekinumab.

## 6.2. Overall Rationale for the Study

Following the assessment of the ustekinumab Periodic Safety Update Report (PSUR) procedure covering the interval from 01 January 2020 to 31 December 2020 (EMEA/H/C/PSUSA/00003085/202012) the EMA/PRAC requested to include 2 additional post-authorization safety studies (PASS's) in the EU-RMP to expand the evidence base on the risk of MACE associated with ustekinumab in patients with PsO and PsA.

The purpose of this study is to aid in addressing the ustekinumab RMP requirement and is part of additional pharmacovigilance activities to address the important potential risk of cardiovascular events (MACE only), within Part III of the RMP, using Swedish national health registries.

Sweden offers excellent administrative databases with universal coverage of the country's population, totaling approximately 10.3 million people. Individual linkage across registers allows for longitudinal studies of large cohorts including data on all their health care visits, diagnoses and procedures, prescribed treatments, long-term sick-leaves, demographics and causes of death. The universal coverage minimizes loss to follow-up and makes cohorts representative to the general population. The registers' completeness and quality are unmatched internationally and make them highly regarded as an evidence base for decision- and policymakers worldwide.

# 7. RESEARCH QUESTION AND OBJECTIVES

**Research Question**

This study will estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with STELARA (ustekinumab) relative to patients initiating treatment with etanercept, adalimumab, and secukinumab in routine clinical practice in Sweden.

**Objective(s) and Measure(s) of Interest**

The primary objective is to estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with ustekinumab relative to patients initiating treatment with etanercept in routine clinical practice in Sweden.

The secondary objectives are to:

- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with ustekinumab relative to patients initiating treatment with adalimumab in routine clinical practice in Sweden
- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with ustekinumab relative to patients initiating treatment with secukinumab in routine clinical practice in Sweden
- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with adalimumab relative to patients initiating treatment with etanercept in routine clinical practice in Sweden
- Estimate and compare the risk of MACE in PsO and PsA patients initiating treatment with secukinumab relative to patients initiating treatment with etanercept in routine clinical practice in Sweden

The outcomes of interest are:

- MACE (composite outcome of myocardial infarction, ischemic stroke, and CV death), as measured by:

  Stabilized propensity score-weighted hazard ratios (primary endpoint)

  Cumulative incidence, unadjusted (secondary endpoint)

  Incidence rates, unadjusted (secondary endpoint)

  - Incidence rates will also be estimated for each component of MACE

**Hypothesis**

This is a study to document the use of ustekinumab and other biologics of interest in PsO and PsA patients. The study aims to describe the data for MACE as it relates to treatment with ustekinumab as part of a PASS. The null hypothesis is that there is no difference in the risk of MACE with ustekinumab treatment compared to etanercept (or adalimumab or secukinumab).

# 8. RESEARCH METHODS

## 8.1. Study Design

### 8.1.1. Overview of Study Design

This is a non-interventional database study based on secondary use of data. This observational cohort study on the cardiovascular safety of ustekinumab relative to etanercept, adalimumab, and secukinumab, based on a new-user design, will use patient-level data from Swedish population-based national registers. The study population of interest is adult (≥18 years of age) patients with PsO and/or PsA diagnosed in secondary care initiating treatment with ustekinumab or etanercept, adalimumab or secukinumab in routine clinical practice in Sweden. The outcome of interest is MACE.

Patients will be allocated to mutually exclusive incident user cohorts based on the first study drug initiated during the study inclusion period. The ustekinumab cohort will consist of patients initiating ustekinumab as the first of the drugs under study ("cohort-defining biologic") during the study inclusion period. The etanercept cohort will consist of patients initiating etanercept as the first of the drugs under study during the study inclusion period, etc. The ustekinumab cohort will be compared to each respective other cohort of etanercept (primary objective), adalimumab, and secukinumab (secondary objective) incident users. To further contextualize the results from the ustekinumab comparisons, the adalimumab and secukinumab cohorts will also be compared to the etanercept cohort.

The new-user treatment cohorts will be analyzed in the context of two populations: the bio-naïve population and the overall incident user population. The bio-naïve population will only include patients initiating a treatment with a cohort-defining biologic who have not been previously treated with any biologic, based on all available dispensation data. The overall incident user population will include patients initiating treatment with a cohort-defining biologic who may or may not have previously been treated with another biologic.

The main analysis will compare ustekinumab to etanercept, adalimumab and secukinumab bio-naïve populations using an intention-to-treat (ITT) definition of exposure time (time at risk), in which patients who discontinue the index biologic will continue to be followed based on their index treatment. Additional analyses of the treatment cohorts will analyze the overall incident user population using an ITT definition of exposure time, and both bio-naïve and overall incident user populations using an as-treated definition of exposure time.

Descriptive statistics will be reported for patient characteristics, covering demographic and clinical characteristics, comorbidities, comedication use, and CV risk factors, for each treatment cohort. Risk of MACE will be analyzed using cumulative incidence estimation and incidence rates for unadjusted risk. A Cox proportional hazards (time-to-event) model with stabilized inverse probability of treatment weighting (IPTW) by propensity scores will be used to adjust for measured confounding by treatment selection, in addition to the confounding addressed by the active-comparator new-user design. The following endpoints will be reported: 1) cumulative incidence (estimated probability) of MACE (with corresponding 95% confidence intervals) within 6, 12, 24, 36, 48, 60 and 72 months of index date, and beyond if possible, together with cumulative incidence curves over the entire available follow-up; 2) incidence rates of MACE during follow-up (with corresponding 95% confidence intervals); and 3) propensity score weighted hazard ratios of MACE (with corresponding 95% confidence intervals) for ustekinumab use compared to use of each of the respective other biologics of interest as well as for adalimumab and secukinumab use compared to etanercept.

Table 1 below summarizes the analyses to be performed, including the populations of interest, definitions of exposure time to be used, and the endpoints analyzed, for each objective.

**Table 1: Summary of Analyses**

| **Primary Objective: Ustekinumab vs. Etanercept** | | | |
|---|---|---|---|
| | **Population** | **Exposure Time Definition** | **Endpoint** |
| **Main Analysis** | Bio-naïve | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Analyses** | Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Bio-naïve | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Overall Incident | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Sensitivity Analysis** | | | |
| • Expanded MACE | Bio-naïve; Overall Incident | ITT; As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • ITT with 2-year cap | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • Study end on Dec 31 2019 | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |

| **Secondary Objective: Ustekinumab vs. Adalimumab** | | | |
|---|---|---|---|
| | **Population** | **Exposure Time Definition** | **Endpoint** |
| **Main Analysis** | Bio-naïve | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Analyses** | Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Bio-naïve | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Overall Incident | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Sensitivity Analysis** | | | |
| • Expanded MACE | Bio-naïve; Overall Incident | ITT; As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • ITT with 2-year cap | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • Study end on Dec 31 2019 | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Objective: Ustekinumab vs. Secukinumab** | | | |
| | **Population** | **Exposure Time Definition** | **Endpoint** |
| **Main Analysis** | Bio-naïve | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Analyses** | Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Bio-naïve | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Overall Incident | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Sensitivity Analysis** | | | |
| • Expanded MACE | Bio-naïve; Overall Incident | ITT; As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • ITT with 2-year cap | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • Study end on Dec 31 2019 | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Objective: Adalimumab vs. Etanercept** | | | |
| | **Population** | **Exposure Time Definition** | **Endpoint** |
| **Main Analysis** | Bio-naïve | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |

| | | | |
|---|---|---|---|
| **Secondary Analyses** | Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Bio-naïve | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Overall Incident | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Sensitivity Analysis** | | | |
| • Expanded MACE | Bio-naïve; Overall Incident | ITT; As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • ITT with 2-year cap | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • Study end on Dec 31 2019 | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Objective: Secukinumab vs. Etanercept** | | | |
| | **Population** | **Exposure Time Definition** | **Endpoint** |
| **Main Analysis** | Bio-naïve | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Secondary Analyses** | Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Bio-naïve | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| | Overall Incident | As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| **Sensitivity Analysis** | | | |
| • Expanded MACE | Bio-naïve; Overall Incident | ITT; As-treated | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • ITT with 2-year cap | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |
| • Study end on Dec 31 2019 | Bio-naïve; Overall Incident | ITT | Cumulative Incidence, Incidence Rates, IPTW Hazard Ratios |

Only data available within clinical practice will be analyzed in this study.

The requirement for patient information and consent has been waived for this study, as it relies solely on deidentified extracts from secondary data sources, with no unique key or identifier on a patient-level available to the research team.

### 8.1.2. Rationale for Study Design Elements

Study design aspects and analysis methods to be implemented are intended to reduce the potential for bias in the study. The active-comparator incident user design mitigates confounding bias by treatment indication, healthy user, and frailty. The bio-naïve requirement in the primary analysis reduces the risk of misattribution of events related to previous treatment exposures to the exposures under study. In addition, propensity score weighting will be used to improve balance between the

comparator cohorts with respect to a wide number of covariates related to exposure and the outcome of interest.

Sweden offers excellent administrative databases with universal coverage of the country's population, totaling approximately 10.3 million people. Individual linkage across registers allows for longitudinal studies of large cohorts including data on all their health care visits, diagnoses and procedures, prescribed treatments, long-term sick-leaves, demographics and causes of death. Thanks to this, sample size is maximized and bias associated with sampling is avoided. The latter is a clear advantage when comparing with data such as claims, where e.g. uninsured patients are not represented and are likely to have different behavior. In the Swedish registries, patients are only lost to follow-up if they emigrate, which means that patients are not lost to follow-up as would be expected when using claims or similar datasets. The universal coverage also makes cohorts representative to the general population. The registers' completeness and quality are unmatched internationally and make them highly regarded as an evidence base for decision- and policymakers worldwide.

The Swedish Prescribed Drug registry (PDR) records all dispensed prescription data, so that there is no missing patient pharmacy dispensation.

The Social Security Number (SSN) of Swedish patients enables the linkage of several different data sources in this study, enabling a wide range of prognostic factors to be included. Since patients have been followed historically in the national Swedish registries for many years, this allows for accurate estimation of patient history including comorbidities, prescription experience, and disease onset. The universal coverage minimizes loss to follow-up and makes cohorts representative to the general population. Thus, the Swedish data conditions are suited to this type of research as they include up to date information on the entire Swedish population.

## 8.2. Setting and Patient Population

### 8.2.1. Study Setting and Duration

The study population of interest is adult (≥18 years of age) patients with PsO and/or PsA diagnosed in secondary care initiating treatment with ustekinumab or a comparator biologic of interest (adalimumab, etanercept, secukinumab). Date of disease onset for PsO/PsA patients will be identified through the first observed PsO/PsA International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes L40.0-4, L40.8-9/L40.5, M07.0-3 in the primary position from 1 January 2001 to 30 December 2021 and dispensations will be identified using Anatomical Therapeutic Chemical (ATC) codes. The date when a patient initiates (i.e. first ever dispensation of) one of the study drugs during the study inclusion period, defined as 1 July 2009 to 30 December 2021, is defined as the patient's index date. The start of the inclusion period is set to 1 July 2009 as ustekinumab was reimbursed in Sweden end of June 2009.

The end of the study period corresponds to the registry data extraction date (31 December 2021) for all patients except for patients registered in region PPD at index date. Public procurement of medicines used in hospitals is carried out by the regional councils in Sweden. The PPD regional council have a procurement agreement for ustekinumab, resulting in a lower-than-list price and

the distribution of the drug through the region's own distribution channels, i.e. hospitals, rather than through private pharmacies since 1 January 2016. This means that ustekinumab is generally not prescribed in PPD, and its use is not fully captured in the Prescribed Drug Register. Thus, there will be incomplete data on ustekinumab use in PPD in the database. For patients living in PPD, the inclusion period will thus run from 1 July 2009 to 31 December 2015. Similarly, in the secondary analysis in which an as-treated exposure definition will be used (see Section 8.3.1.1), these patients will be censored on 31 December 2015, instead of 31 December 2021. Without this rule for patients living in PPD, analyses can result in unobserved switch events from other biologics to ustekinumab, and unobserved true index dates of ustekinumab, for patients registered in region PPD in 2016 onwards.

Note that while the follow-up period will end on 31 December 2021, the inclusion period ends on 30 December 2021 as the data resolution is on the date-level, meaning patients will need to be included prior to 31 December 2021 in order to be included in the planned time-to-event analyses. In addition, access to data covering the years 2020 and 2021 is contingent on timely delivery from the register holder, which is not guaranteed due to the possibility of delays related to the ongoing COVID-19 pandemic. Although deemed unlikely, if timely delivery of data covering 2020 and 2021 is not possible, the study inclusion period and study end dates will be 30 December 2019 and 31 December 2019, respectively.

Patients will be allocated to mutually exclusive incident user cohorts based on the first study drug initiated during the study inclusion period. The ustekinumab (incident user) cohort will consist of patients initiating ustekinumab as the first study drug during the study inclusion period. The etanercept cohort will consist of patients initiating etanercept as the first study drug during the study inclusion period, etc.

### 8.2.2. Selection Criteria

Each potential participant must satisfy the following criteria to be eligible for data collection in this study:

1. Patient must be aged at least 18 years.

2. Patient must have a confirmed diagnosis of PsO/PsA (International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes L40.0-4, L40.8-9/L40.5, M07.0-3) recorded in the primary position (primary diagnosis) between 1 January 2001 and 30 December 2021.

3. The patient must have initiated treatment with one of the cohort-defining biologics during the study inclusion period (1 July 2009 to 30 December 2021).

4. The patient must have lived in Sweden for at least 5 years, to ensure the availability of sufficient historical data at baseline.

Potential participants who meet the following criterion will not be eligible for this study:

1. First ever dispensation of any of the study drugs occurring before the first diagnosis of PsO/PsA will exclude the patient from entering that specific biologic cohort.

The non-eligibility criterion is intended to exclude patients treated with any of the biologics under study for indications other than PsO and PsA.

In addition to the overall eligibility criteria listed above, patients cannot be included in a specific treatment cohort if they have been treated with that biologic prior to the start of the study inclusion period. However, for the overall incident user population, previous use of a biologic does not preclude inclusion in another incident biologic cohort.

## 8.3. Variables

### 8.3.1. Treatment Exposures of Interest

The main exposure of interest is initiation of ustekinumab in the eligible study population. The comparator exposures of interest are initiation of: 1) etanercept; 2) adalimumab; 3) secukinumab. Dose-dependent or dose-duration responses will not be studied in the main or secondary analyses, but will be explored separately (see 8.7.7). Any patient meeting the eligibility criteria who initiates treatment (i.e. first ever dispensation in the available data) with ustekinumab, etanercept, adalimumab, or secukinumab (defined in Table 2) during the study inclusion period, i.e. from 1 July 2009 until 30 December 2021, will thus be included in the study.

The primary comparison will be between ustekinumab and etanercept.

Information will be available on prescription and dispensation date and amount of dispensed drug. Neither the indication for prescribing the drug nor the daily dosage prescribed will be available.

**Table 2: ATC Codes Used in the Definition of Study Exposures**

| Drug Name | ATC Code |
|---|---|
| Ustekinumab | L04AC05 |
| Adalimumab | L04AB04 |
| Etanercept | L04AB01 |
| Secukinumab | L04AC10 |

*Abbreviation: ATC Anatomical Therapeutic Chemical.*

#### 8.3.1.1. Time at Risk

**Primary analysis**

An ITT definition of exposure time (time at risk) will be used in the primary analysis. Exposure time in the primary analysis will be measured from first initiation of treatment with a study drug during the study inclusion period until an event (MACE), (non-CV) death, emigration or end of data availability, whichever comes first.

**Secondary analysis**

In the secondary analysis, an as-treated definition of time at risk will be used. Exposure time in the secondary analysis will thus be measured from first initiation of treatment with a study drug during the study inclusion period until an event (MACE), (non-CV) death, switch to another biologic, discontinuation of the cohort-defining biologic, emigration, end of data availability, or 31 Dec 2015 for patients living in PPD at the index date. In the case of a switch to another biologic, the exposure time of the cohort-defining study drug will end on the date of first dispensation of the biologic the patient switches to.

Sensitivity analyses are described in Section 8.7.6.

**Discontinuation**

To determine discontinuation of the cohort-defining biologic, start and stop of treatment episodes will be defined as follows:

- Start of treatment is defined as the date of first filling of a prescription of a cohort-defining biologic during the study inclusion period.
- Discontinuation of treatment is not registered explicitly in the data but must be inferred by absence of recurrent dosing (or dispensing) after a clinically expected interval. Patients will be considered to have discontinued a cohort-defining drug after the inferred end of a previous dispensation's dispensation interval if 90 days pass with no new dispensation of said drug following the inferred end.

The inferred length of each dispensation will be based on the amount dispensed and recommended maintenance dosing intervals, per Table 3 below.

**Table 3: Maintenance Posology for Biologics in the Treatment of PsO and PsA**

| Drug Name | Maintenance Dosing | Daily dose |
|---|---|---|
| Adalimumab | 40 mg every two weeks | DAILYDOSE = 40/14 |
| Etanercept | 25 mg twice every week or 50 mg every week | DAILYDOSE = 50/7 |
| Ustekinumab | 45 or 90 mg once every 12 weeks<br>Weight ≤ 100 kg: 45 mg<br>Weight > 100 kg: 90 mg | DAILYDOSE = 45/84 if STYRKALF= "45 mg"<br>DAILYDOSE = 90/84 if STYRKALF= "90 mg" |
| Secukinumab | 300 mg once monthly | DAILYDOSE = 300/28 |

### 8.3.2. Outcomes

The primary outcome of interest is incident MACE, defined as any of cardiovascular death, ischemic stroke (IS), and/or myocardial infarction (MI). Analyses will be of first event during follow-up only.

MI and IS events are defined as hospitalizations or outpatient hospital visits with a primary diagnosis code for MI or IS (Table 4). For hospitalizations, a minimum of 30 days will be required

between events of the same type to be counted as separate events; this rule has been used to define CV events in several published studies based on the same underlying register data [15, 16]. Note that as the analysis will be of time-to-first-event, this will only matter in cases of MACE within the 30 days prior to index date. Further, for MACE diagnoses in the outpatient setting, a recall period (washout period) of 6 months will be applied. If the patient had any in- or outpatient primary diagnosis of MACE in the 6 months before the outpatient MACE diagnosis, the MACE diagnosis recorded in the outpatient setting will be censored to prevent misclassification and double counting of a follow-up diagnosis.

Cardiovascular death is defined based on ICD codes for underlying cause of death.

Non-CV death will be treated as a competing risk in the estimation of cumulative incidence of MACE. Deaths with no CV ICD codes are considered non-CV deaths.

The outcomes are identified from start of follow-up (index date) to first occurrence in the data, based on the definitions above.

**Table 4: Codes Used in the Definition of MACE**

| CV event | Type of code | Code |
|---|---|---|
| Myocardial infarction | ICD-10 | I21 |
| Ischemic stroke | ICD-10 | I63-I64 |
| CV death | Codes for underlying cause of death in the CDR, based on ICD-10 | I chapter (I00-I99) |

### 8.3.3. Patient Characteristics at Baseline

The baseline variables related to patient characteristics to be summarized at index date (date of first prescription of study drug), grouped by whether the variable is continuous (CON) or categorical (CAT), are listed below. Each drug cohort will be summarized separately, for both populations of interest (overall incident user and bio-naïve populations).

Baseline (dispensation index date) variables:

- Age is defined as age in years at index date (CON)
- Sex is defined as male or female at index date (CAT)
- Time since disease onset, in years (CON)
- Index year (2009-2021) (CAT)
- Follow-up time, in years (CON)
- Region of residence is defined as patient's registered region (county) of residence at index date (CAT)
- PsO/PsA indicated biologic/Janus kinase (JAK)-inhibitor experience at index is defined based on any dispensation in the available data (going back to 1 July 2005) of the biologic/JAK-inhibitor drugs (Table 5) before index date (CAT)

- PsO/PsA indicated biologic/JAK-inhibitor line at index is defined as the number of different biologic/JAK-inhibitor drugs (Table 5) dispensations in the available data (going back to 1 July 2005) before the index date (CON)
- TNF inhibitor experience is defined as exposure to a TNF inhibitor (Table 5) based on dispensations in the available data (going back to 1 July 2005) before the index date (CAT)
- IL inhibitor experience is defined as exposure to an IL inhibitor (Table 5) based on dispensations in the available data (going back to 1 July 2005) before the index date (CAT)
- JAK-inhibitor experience is defined as exposure to a JAK-inhibitor (Table 5) based on dispensations in the available data (going back to 1 July 2005) before the index date (CAT)
- The sum of the number of inpatient stays and outpatient visits for PsO or PsA (based on primary diagnoses) during the five years prior to and including index date (CON)
- Education level is defined at index date based on the highest level of education attained in the year prior to index or closest to index if not available the year prior to index (CAT), based on the following categories
    1. <upper secondary education
    2. upper secondary education
    3. >upper secondary school
    4. first stage tertiary education bachelor or equivalent
    5. first stage tertiary education master or equivalent
    6. second stage tertiary education PhD or equivalent
- Marital status is defined at index date as MARRIED 1 if record of Married or Registered Partnership, using the closest observation before or at index date (CAT)
- Presence of PsO is defined as having a ICD-10 code for PsO at any time prior to (going back to 2001) and including index date (Table 6) (CAT)
- Presence of PsA is defined as having a ICD-10 code for PsA prior to (going back to 2001) and including index date (Table 6) (CAT)
- Presence of Crohn's disease, based on ICD-10 codes from the five years prior to and including index date (Table 6) (CAT)
- Presence of ulcerative colitis based on ICD-10 codes from the five years prior to and including index date (Table 6) (CAT)
- Presence of uveitis based on ICD-10 codes from the five years prior to and including index date (Table 6) (CAT)
- Presence of diabetes mellitus (yes 1, no 0) based on dispensations of antidiabetic drugs during the 1-year period before and including index date and/or a diagnosis code of diabetes during the 5-year period prior to and including index date (Table 6) (CAT)
- Presence of hypertensive disease based on dispensations of antihypertensive drugs during the year (365 days) prior to and including index date (CAT) (Table 6)

- Presence of dyslipidemia (yes 1, no 0) based on dispensations of hypolipidemic drugs during the 1-year period before and including index date and/or a diagnosis code of disorders of lipoprotein metabolism and other lipidaemias during the 5-year period prior to and including index date (Table 6) (CAT)
- Use of nicotine replacement therapy based on dispensations with ATC code N07BA during the year (365 days) prior to and including index date (CAT)
- Use of NSAIDs based on dispensations with ATC code M01A during the year (365 days) prior to and including index date (CAT)
- History of obesity based on ICD-10 and Klassifikation av vårdåtgärder (Swedish medical procedure) codes from the five years prior to and including index date (Table 6) (CAT)
- Presence of chronic obstructive pulmonary disease (COPD) based on ICD-10 codes from the five years prior to and including index date (Table 6) (CAT)
- Diagnosis of COVID-19 based on ICD-10 codes from the five years prior to and including index date (Table 6) (CAT)
- Documented cardiac or systemic atherosclerotic vascular disease (peripheral arterial disease, coronary artery disease, cerebrovascular disease, past revascularization procedures) based on ICD-10 and Klassifikation av vårdåtgärder (Swedish medical procedure) codes from the five years prior to and including index date (Table 6) (CAT)
- High risk of CV disease based on either prior MACE (defined per the outcome definition) at some point during the five years prior to and including index date, OR at least two of the following risk factors (CAT):
    1. Age >50 years for men, >60 years for women
    2. COPD and/or nicotine replacement therapy (defined as above) as proxy for smoking
    3. Obesity, defined as above, i.e. as either:
        a. History of obesity based on ICD-10 codes E66 from the five years prior to and including index date (Table 6); OR
        b. Bariatric surgery based on Klassifikation av vårdåtgärder (Swedish medical procedure) codes JDF from the five years prior to and including index date
    4. Diabetes mellitus, defined as above, i.e. as either:
        a. Presence of diabetes mellitus based on ICD-10 codes E10-E14 from the five years prior to and including index date; OR
        b. Use of antidiabetic drugs based on dispensations with ATC code A10A or A10B during the year (365 days) prior to and including index date
    5. Hypertensive disease, defined as above
    6. Dyslipidemia, defined as above, i.e. as either:
        a. Presence of disorders of lipoprotein metabolism and other lipidaemias based on ICD-10 code E78 from the five years prior to and including index date; OR

b. Use of hypolipidemic agents based on dispensations with ATC codes C10AA, C10AB, C10AX, or C10B during the year (365 days) prior to and including index date

- History of MACE (same definition as above but reported as a separate variable) (CAT)
- Charlson Comorbidity Index based on diagnosis codes during the five years prior to and including index date (CON)
- Use of non-biologic immunomodulators (methotrexate, cyclosporine, mycophenolate, apremilast, fumaric acid, oral retinoids, oral glucocorticoids, sulfasalazine, leflunomide, or oral tacrolimus) based on dispensations during the year (365 days) prior to and including index date (CAT)
- Use of phototherapy during the year (365 days) prior to and including index date (CAT)
- Time since last dispensation of a biologic other than the cohort-defining biologic, for patients with such a dispensation within the 6 months (183 days) prior to index date (overall incident user cohort only) (CON), in order to inform on the extent to which outcome events could theoretically be related to previous biologic exposures in the overall incident user cohort

In addition to the baseline variables listed above, the number and percentage of patients treated with immunomodulators during follow-up as well as the median time of exposure to the cohort-defining biologic during follow-up in the ITT analysis will be reported. Further, the number and percentage of patients who die within 30 days from a hospitalization of MI or IS will also be reported.

**Table 5: Codes Used in the Definition of PsO/PsA Indicated Biologic/JAK-inhibitors**

| Drug | Type of code | Code | Group |
|---|---|---|---|
| Abatacept | ATC | L04AA24 | None |
| Adalimumab | ATC | L04AB04 | TNF inhibitor |
| Brodalumab | ATC | L04AC12 | IL inhibitor |
| Certolizumab pegol | ATC | L04AB05 | TNF inhibitor |
| Etanercept | ATC | L04AB01 | TNF inhibitor |
| Golimumab | ATC | L04AB06 | TNF inhibitor |
| Guselkumab | ATC | L04AC16 | IL inhibitor |
| Infliximab | ATC | L04AB02 | TNF inhibitor |
| Ixekizumab | ATC | L04AC13 | IL inhibitor |
| Risankizumab | ATC | L04AC18 | IL inhibitor |
| Secukinumab | ATC | L04AC10 | IL inhibitor |
| Tildrakizumab | ATC | L04AC17 | IL inhibitor |
| Tofacitinib | ATC | L04AA29 | JAK-inhibitor |
| Upadacitinib | ATC | L04AA44 | JAK-inhibitor |
| Ustekinumab | ATC | L04AC05 | IL inhibitor |

**Table 6: Codes Used in the Definition of Other Variables of Interest**

| Variable | Type of code | Code |
|---|---|---|
| Charlson Comorbidity Index | ICD-10 | See Table 14 |
| Antihypertensive drugs | ATC | C02, C03, C07-09 |
| Presence of PsO | ICD-10 | L40.0-4, L40.8-9 |
| Presence of PsA | ICD-10 | L40.5, M07.0-3 |
| Presence of Crohn's disease | ICD-10 | K50 |
| Presence of ulcerative colitis | ICD-10 | K51 |
| Presence of uveitis | ICD-10 | H20 |
| Presence of diabetes mellitus | ICD-10 | E10-E14 |
| History of obesity | ICD-10 and Klassifikation av vårdåtgärder (Swedish medical procedures) codes | Obesity, ICD-10: E66<br>Bariatric surgery, Klassifikation av vårdåtgärder (Swedish medical procedures) codes: JDF |
| Chronic obstructive pulmonary disease | ICD-10 | J41-J44 |
| COVID-19 | ICD-10 | U07 |
| Documented cardiac or systemic atherosclerotic vascular disease | ICD-10 and Klassifikation av vårdåtgärder (Swedish medical procedures) codes | Peripheral arterial disease, ICD-10: I70.0, I70.2, I73.9<br>Coronary artery disease, ICD-10: I20-I25<br>Cerebrovascular disease, ICD-10: per Charlson comorbidity index, see Table 18<br>Revascularizations, Klassifikation av vårdåtgärder (Swedish medical procedures) codes: FNA, FNB, FNC, FND, FNE, FNF, FNG, FNW |
| Use of non-biologic immunomodulators | ATC | Methotrexate: L01BA01<br>Cyclosporine: L04AD01<br>Mycophenolate: L04AA06<br>Leflunomide: L04AA13<br>Apremilast: L04AA32<br>Oral tacrolimus: L04AD02<br>Oral glucocorticoids: H02AB<br>Sulfasalazine: A07EC01<br>Antipsoriatics for systemic use: D05B |
| Use of phototherapy | Klassifikation av vårdåtgärder (Swedish medical procedures) codes | "Ljusbehandling, UVA": DQ012<br>"Ljusbehandling, UVA1": DQ013<br>"Ljusbehandling, UVB": DQ014<br>"Ljusbehandling, UVB och UVA": DQ016 |

### 8.3.4. Strata-defining Variables

Outcomes will be generated separately for each drug cohort. In addition, the following patient stratifications are of specific interest:

- Presence of PsO alone vs. presence of PsO (with or without PsA) vs. presence of PsA (with or without PsO)
- High vs. low ("not high") CV risk

All stratifications will be analyzed separately for each treatment cohort, i.e. as stratifications within each respective drug cohort, for both the overall incident user population and the bio-naïve population, where sample size allows. The stratifications will be analyzed using both the primary exposure definition (ITT) and the as-treated exposure definition.

### 8.3.5. Variable Summary

Table 7 provides an overview and summary of variables of interest in the study based on the information in the preceding subsections.

**Table 7: Variable Overview and Summary Table**

| **Study population defining variables** | **Definition** | **Data period** |
|---|---|---|
| Psoriasis diagnosis | ICD-10: L40.0-4, L40.8-9 | 1 Jan 2001 – 30 Dec 2021 |
| Psoriatic arthritis diagnosis | ICD-10: L40.5, M07.0-3 | 1 Jan 2001 – 30 Dec 2021 |
| **Study population defining variables** | **Definition** | **Data period** |
| Psoriasis diagnosis | ICD-10: L40.0-4, L40.8-9 | 1 Jan 2001 – 30 Dec 2021 |
| Psoriatic arthritis diagnosis | ICD-10: L40.5, M07.0-3 | 1 Jan 2001 – 30 Dec 2021 |
| **Exposure(s)** | | |
| Ustekinumab | ATC: L04AC05 | 1 July 2009 – 30 Dec 2021 |
| Etanercept | ATC: L04AB01 | 1 July 2009 – 30 Dec 2021 |
| Adalimumab | ATC: L04AB04 | 1 July 2009 – 30 Dec 2021 |
| Secukinumab | ATC: L04AC10 | 1 July 2009 – 30 Dec 2021 |
| **Outcomes(s)** | | |
| Myocardial infarction | ICD-10: I21 | 2 July 2009 – 31 Dec 2021 |
| Ischemic stroke | ICD-10: I63-I64 | 2 July 2009 – 31 Dec 2021 |
| CV death | Codes for underlying cause of death in the Cause of Death Register, based on the ICD-10 I chapter | 2 July 2009 – 31 Dec 2021 |
| **Covariates** | | |
| Age | Age in years | At baseline (index) |
| Sex | Male/Female | At baseline (index) |
| Region of residence | Living county | At baseline (index) |
| Time since disease onset | Time since disease onset in years | 1 Jan 2001 to index |
| Index year | Calendar year at index | At baseline (index) |

| | | |
|---|---|---|
| Education level | Highest education level attained the year prior to index year | At baseline (index), based on data from the calendar year prior to index or closest to index if not available the year prior to index |
| Marital status | Married or Registered Partnership | At baseline (index), based on data from the calendar year prior to index or closest to index if not available the year prior to index |
| Biologic/JAK-inhibitor experience | ATC: L04AA24, L04AA29, L04AA44, L04AB01, L04AB02, L04AB04, L04AB05, L04AB06, L04AC10, L04AC12, L04AC13, L04AC16, L04AC17, L04AC18 | 1 July 2005 to index date |
| Biologic/JAK-inhibitor treatment line | | |
| TNF-inhibitor experience | ATC, Table 5 | |
| IL-inhibitor experience | | |
| JAK-inhibitor experience | | |
| The sum of the number of inpatient stays and outpatient visits for PsO or PsA (proxy for disease severity) | ICD-10: L40.0-5, L40.8-9, M07.0-3 | Five years prior to, and including, index date |
| Charlson comorbidity index | ICD-10 codes, Table 14 | Five years prior to, and including, index date |
| Antihypertensive drug use | ATC: C02, C03, C07-09 | One year prior to, and including, index date |
| Nicotine replacement therapy | ATC: N07BA | One year prior to, and including, index date |
| Use of NSAIDs | ATC: M01A | One year prior to, and including, index date |
| Presence of Crohn's disease | ICD-10: K50 | Five years prior to, and including, index date |
| Presence of ulcerative colitis | ICD-10: K51 | Five years prior to, and including, index date |
| Presence of uveitis | ICD-10: H20 | Five years prior to, and including, index date |
| Presence of diabetes mellitus | ICD-10: E10-E14 | Five years prior to, and including, index date |
| History of obesity | At least one of the following:<br>• Obesity, ICD-10: E66<br>• Revascularizations, Klassifikation av vårdåtgärder (Swedish medical procedures) codes: JDF | Five years prior to, and including, index date |
| Chronic obstructive pulmonary disease | ICD-10: J41-J44 | Five years prior to, and including, index date |

| | | |
|---|---|---|
| COVID-19 | ICD-10: U07 | Five years prior to, and including, index date |
| Documented cardiac or systemic atherosclerotic vascular disease (peripheral arterial disease, coronary artery disease, cerebrovascular disease, past revascularization procedures) | At least one of the following:<br>• Peripheral arterial disease, ICD-10: I70.0, I70.2, I73.9<br>• Coronary artery disease, ICD-10: I20-I25<br>• Cerebrovascular disease, ICD-10: per Charlson comorbidity index, see Table 14<br>• Revascularizations, Klassifikation av vårdåtgärder (Swedish medical procedures) codes: FNA, FNB, FNC, FND, FNE, FNF, FNG, FNW | Five years prior to, and including, index date |
| Dyslipidemia | At least one of the following:<br>• Use of hypolipidemic agents, ATC: C10AA, C10AB, C10AX, C10B<br>• Presence of disorders of lipoprotein metabolism and other lipidaemias, ICD-10: E78 | One year prior to, and including, index date<br>Five years prior to, and including, index date |
| History of MACE | Per the outcome definition | Five years prior to, and including, index date |
| Use of non-biologic immunomodulators | Methotrexate, cyclosporine, mycophenolate, apremilast, fumaric acid, oral retinoids, oral glucocorticoids, sulfasalazine, leflunomide, or oral tacrolimus during the 1-year period before index date | One year prior to, and including, index date |
| Use of phototherapy | Klassifikation av vårdåtgärder (Swedish medical procedures) codes DQ012, DQ013, DQ014, DQ016 | One year prior to, and including, index date |
| **Strata-defining variables** | | |
| High risk of CV disease | See section 8.3.3 for definition | See section 8.3.3 for definition |
| Presence of PsO alone vs. presence of PsO (with or without PsA) vs. presence of PsA (with or without PsO) | See above | See above |

## 8.4. Data Sources

The data source for the study are Swedish national population-based registers. Data for all patients with a PsO diagnosis (ICD-10 L40+, i.e. including PsA [L40.5], OR M07.0-3 OR ICD-8/9 code of 696) recorded before 31 December 2021 in specialist care in Sweden, will be extracted from the registers held by the National Board of Health and Welfare (NBHW) (Table 8). All data will be pseudonymized and will be submitted to Quantify with study specific subject-ids for linkage between datasets.

**Table 8: Summary of Key Data sources Used in the Study**

| Type of Data | Source Registry | Details |
|---|---|---|
| Inpatient care | National Patient Registry (NPR) | Includes the dates and associated diagnoses for all inpatient specialist care in Sweden, as well as demographics such as patient age and sex. Data are available from 1964 and onwards. |
| Outpatient care | National Patient Registry (NPR) | Includes the dates and associated diagnoses with all outpatient specialist care in Sweden, as well as demographics such as patient age and sex. Data are available from 2001 and onwards. |
| Prescriptions | Prescribed Drug Registry (PDR) | All prescriptions dispensed by patients at Swedish pharmacies are included in this registry. The data includes date of prescription and dispensation, formulation, amount dispensed, defined daily dose (DDD), and others from July 2005 and onwards. |
| Mortality | Cause of Death Registry (CDR) | Includes the cause and date of all deaths in Sweden, from 1952 and onwards. |

The data sources to be used in the study are national health registers to which reporting is mandatory and therefore exhibit close to complete coverage of individuals in Sweden

A recent validation study based on medical records of information in the PDR on dispensations of injection biologics, such as those defining exposure in this study, report sensitivities of >85% [21].

Validation studies of the inpatient part of the NPR, report positive predictive values of 85-95% for the diagnosis data [22]. For MI and stroke (including transient ischemic attacks) specifically, positive predictive values of 98-100% and 98.6% were reported.

High agreement between underlying cause of death in the Swedish CDR and systematically reviewed medical records has been reported for several specific diseases, including cardiovascular disease (>85%) [23].

## 8.5. Study Size

As this study uses national registry data, sample size is maximized and cannot be increased.

The projected number of patients to be analyzed in the primary objective using the primary analysis definitions is ~580 bio-naïve ustekinumab initiators and ~5400 bio-naïve etanercept initiators. These projections are based on the number of bio-naïve ustekinumab and etanercept initiators observed in a similar analysis based on the same underlying register data, covering data until and

including 2019 (investigator data on file). Further, publicly available data from the Swedish National Board of Health and Welfare on the total number of patients with dispensations for the study drugs of interest (all indications) between 2009 and 2020 (see Table 9 below) have informed 1) the expected amount of follow-up for each treatment cohort, 2) the assumption that the adalimumab and etanercept cohorts are approximately equal in size, and 3) the number of additional patients to be included based on the addition of data from 2020 and 2021.

**Table 9: Number of Patients with Dispensations of Study Drugs, 2009-2020**

| Treatment | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adalimumab | 5427 | 6368 | 7093 | 7775 | 8487 | 9239 | 10161 | 10860 | 11530 | 12592 | 18236 | 13494 |
| Etanercept | 7315 | 7744 | 7841 | 7845 | 8162 | 8786 | 9298 | 10758 | 12561 | 14500 | 14086 | 22285 |
| Ustekinumab | 14 | 74 | 161 | 221 | 322 | 516 | 759 | 808 | 1044 | 1362 | 1705 | 2079 |
| Secukinumab | 0 | 0 | 0 | 0 | 0 | 0 | 103 | 873 | 1495 | 1857 | 2011 | 2194 |

*Source: [24]*

Power calculations were performed for the primary comparison of ustekinumab vs. etanercept and primary population of interest (the bio-naïve population) based on the primary exposure time definition (ITT). The background rate for MACE has been estimated to ~9.5 per 1000 patient-years in populations of patients using etanercept for PsO/PsA [25]. Assuming the same background rate, a non-time-dependent risk of events, and a ratio of ustekinumab and etanercept subjects of 580:5400 with a mean follow-up of 3 and 4 years, respectively, and using a type I error rate of 0.05, the smallest effect size that can be detected with a preserved power of 80% would correspond to a hazard ratio of 1.9, based on the method described by Schoenfeld [26].

## 8.6. Data Management

The NBHW continuously validates the information in order to ensure that data are complete, comprehensive and of highest possible quality. Data will be examined for completeness before beginning the analysis.

Data management will be carried out in logical steps by the lead programmer. This study will use R and/or STATA 16 (PPD ) to perform the statistical analyses and produce graphics. Separate programs will be developed for data cleaning, variable derivation, and analysis in a structured way. Each program will consist of a header with the following information:

- Author
- Date
- Purpose
- Data sets used
- Data sets produced
- Output produced (e.g. CSV files)
- Revision history

Logs will be generated for each programming and reviewed for errors. Programs will be reviewed by a second programmer to validate the statements used and output produced during the data management and analysis phases. Overall, the data management phase will follow general good programming practices.

## 8.7. Data Analysis

Statistical analyses will be performed by or under the authority of the investigator. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections.

### 8.7.1. Descriptive Analysis

Descriptive statistics will be reported for patient characteristics, prescriptions, and study outcomes (MACE, MI, IS, CV death). Risk of MACE will be analyzed using cumulative incidence estimation and incidence rates with 95% confidence intervals for unadjusted risk.

### 8.7.2. Propensity Scores and Inverse Probability of Treatment Weighting

To reduce confounding by treatment selection, beyond the confounding addressed by the new-user active-comparator design, a Cox proportional hazards (time-to-event) model with stabilized IPTW by propensity scores will be used to adjust for measured confounding by treatment selection.A robust variance estimator will be used to account for the within-subject correlation introduced through the weighting. Stabilized weights will be used to reduce variability induced by subjects with large weights and calculated by multiplying the IPTW by the proportion of treated or untreated patients depending on the treatment status of the patient.

#### 8.7.2.1. Estimating the Propensity Scores

The propensity score for each patient will be estimated using multivariable logistic regression analysis, in which the outcome is set as the treatment assigned. The propensity score will be calculated as the predicted probability of initiating the exposure of interest, i.e. ustekinumab (and adalimumab/secukinumab in the relevant secondary objectives).

The covariates to be included in the propensity score model are those available in the data and identified as potential confounders (related to treatment and outcome) or as simply prognostic of outcome, as the latter increase the precision of the model [27]. Variables identified as such that will be considered for inclusion in the estimation of the propensity score are specified in this protocol and will not be identified based on statistical hypothesis testing in the analytic sample, in order to separate the design from the analysis phase of the study [28].

Based on the above, the following variables will be considered for inclusion in the logistic model predicting probability of ustekinumab exposure (and adalimumab/secukinumab exposure in the relevant secondary objectives) (final list to be included in report):

- Age (years) (at index)
- Female (yes 1, no 0) (at index)

- Index year (year 2009 0/1, year 2010 0/1, and so on) (at index)
- Diabetes mellitus (yes 1, no 0) (based on dispensations of antidiabetic drugs during the 1-year period before index and/or a diagnosis code of diabetes during the 5-year period before index)
- Charlson Comorbidity Index (based on data from the 5-year period before index)
- PsO/PsA indicated biologic/JAK-inhibitor line (treatment line 1 0/1, treatment line 2 0/1, treatment line 3 0/1, treatment line >3 0/1) (at index)
- TNF inhibitor experience based on dispensations in the available data before the index date (going back to 1 July 2005)
- IL inhibitor experience based on dispensations in the available data before the index date (going back to 1 July 2005)
- JAK-inhibitor experience based on dispensations in the available data before the index date (going back to 1 July 2005)
- The sum of the number of inpatient stays and outpatient visits for PsO or PsA, as a proxy for disease severity (during 5-year period before index)
- Education level is defined at index date based on the highest level of education attained in the year prior to index or closest to index if not available the year prior to index (CAT), based on the following categories

  <upper secondary education

  upper secondary education

  >upper secondary education

  first stage tertiary education bachelor or equivalent

  first stage tertiary education master or equivalent

  second stage tertiary education PhD or equivalent
- Marital status (married 1, not married 0) (at index)
- Presence of PsA (yes 1, no 0) (at any time before index)
- History of MACE (yes 1, no 0) (during 5-year period before index)
- Hypertension (yes 1, no 0) (based on dispensations of antihypertensive drugs during the 1-year period before index)
- Dyslipidemia (yes 1, no 0) (based on dispensations of hypolipidemic agents during the 1-year period before index and/or a diagnosis code of disorders of lipoprotein metabolism and other lipidaemias during 5-year period before index)
- Obesity (yes 1, no 0) (during 5-year period before index)
- Presence of COPD (yes 1, no 0) (during 5-year period before index)
- Diagnosis of COVID-19 (yes 1, no 0) (during 5-year period before index)

- Use of nicotine replacement therapy (yes 1, no 0) (based on dispensations during the 1-year period before index date)
- Use of NSAIDs (yes 1, no 0) (based on dispensations during the 1-year period before index date)
- Documented cardiac or systemic atherosclerotic vascular disease (yes 1, no 0) (during 5-year period before index)
- Time since disease onset (years) (at index)
- Use of immunomodulators (yes 1, no 0) (based on dispensations during 1-year period before index)
- Use of phototherapy (yes 1, no 0) (during 1-year period before index)

The propensity scores will be used for inverse probability treatment weighting in the Cox proportional hazards regression model. This weighting strategy estimates the average treatment effect. Stabilized weights will be used to reduce variability induced by subjects with large weights. The stabilized weights (including mean, standard deviation, and range) will be assessed to confirm a mean stabilized weight of approximately one and a limited range. In addition, positivity for key confounders will be assessed, with consideration of recategorization when there is non-positivity

#### 8.7.2.2. Balance and Overlap

A key diagnostic when using propensity scores is the balance of confounder variables between the treated cohorts. To assess this, the percentage standardized differences will be calculated for each respective covariate included in the propensity score model, between the comparator cohorts in each respective objective. Standardized differences will be calculated both before and after weighting using the same pooled SD to ensure that reductions in the standardized difference reflect a real increase in balance rather than simply a change in scale due to varying SD. Balance will be considered acceptable if the standardized differences are <10% after weighting. In case of remaining imbalance, the propensity scores will be remodelled (including e.g. interaction terms, higher order terms, or through recategorizing) until balance has been achieved. If balance cannot be achieved even after extensive remodelling, the unbalanced covariates will be included in the final Cox model [30].

The distribution overlap of the propensity scores will be reported graphically for each treatment comparison, to inform on the degree of overlap between the comparator cohorts. In addition, the preference score distribution will be reported for each treatment pair, with pairs considered as emerging from empirical equipoise if at least half of the exposures are to patients with a preference score between 0.3 and 0.7[29].

### 8.7.3. Main Summary Measures

Continuous variable summary tables will report the following statistics:

- Mean
- Median
- Standard deviation (SD) of the mean

- 25th and 75th percentile
- Min
- Max

Categorical variable summary tables will report the following statistics:

- Number of patients in each category
- Percentage of patients in each category

Differences between groups may be evaluated based on standardized differences in means and proportions and may be tested for statistical significance using t-tests for continuous variables, and Pearson's chi-squared test for categorical variables.

The endpoints of interest are cumulative incidence of MACE with death by other causes (non-CV death) accounted for as a competing risk, (person-time) incidence rates of MACE and its respective components per 100 person-years, and propensity score-weighted hazard ratios. Cumulative incidence is defined as the probability that the outcome event has occurred before a given time and is measured as the number of incident events that has occurred up to each point in time (measured in days from index) divided by the number of patients at risk at that point in time. Cumulative incidence curves over the entire available follow-up will be presented. In addition, tables describing the cumulative incidence of MACE at 6, 12, 24, 36, 48, 60, and 72 months follow-up (where available, and beyond if possible) will be generated.

In the propensity score-weighted Cox regression analyses adjusting for differences in baseline characteristics between treatment cohorts, the main measure of effect is the (weighted) hazard ratio of MACE for ustekinumab compared to each other drug cohort of interest.

Results and patient characteristics will be reported separately for each drug cohort. In addition to the results for the overall cohorts, results will also be presented separately for the following subgroups:

- PsO alone (without PsA)
- PsO (with or without PsA)
- PsA (with or without PsO)
- High risk of CVD
- Low ("not high") risk of CVD

The stratifications will be analyzed using both the primary exposure definition (ITT) and the as-treated exposure definition.

### 8.7.4. Main Statistical Methods

Incidence rates and time-to-event analyses will be used to study the risk of MACE. The probability of MACE will be estimated by cumulative incidence functions. A Cox proportional hazards model [31] with stabilized IPTW by propensity scores and a robust variance estimator, modeling on

the cause-specific hazard of MACE, will be estimated to adjust for confounding by treatment selection.

The Cox proportional hazards model relies on the proportional hazards assumption which means that the hazard ratio does not vary with time, except through the possible time variation in the covariates. Under this condition, the logged hazard ratio (HR) can be modeled as Equation 1:

**Equation 1:** $\log[HR(\boldsymbol{x})] = log\frac{h(t|\boldsymbol{x})}{h_0(t)} = \beta_1 x_1 + ... + \beta_p x_p,$

where $h(t|\boldsymbol{x})$ is the hazard function at time $t$ for an observation with covariate value $\boldsymbol{x}$, and $h_0(t)$ is the baseline hazard function, defined as the hazard at time $t$ for observations with all predictors $p$ set equal to zero [32]. Solving the above equation, the HR can be modeled as Equation 2:

**Equation 2:** $HR(\boldsymbol{x}) = \exp\left(\beta_1 x_1 + ... + \beta_p x_p\right).$

The proportional hazards assumption will be tested based on the Schoenfeld residuals. If the assumption is violated, the analyses will be restricted to shorter follow-up periods and HRs instead reported for 0-1, 0-2, and 0-3 years of follow-up.

In addition to the model of the overall populations, separate models will be run and presented for the following subgroups using both the primary exposure definition (ITT) and the as-treated exposure definition:

- PsO alone (without PsA)
- PsO (with or without PsA)
- PsA (with or without a PsO diagnosis)
- High risk of CVD
- Low ("not high") risk of CVD

For each parameter in the model, the following output will be reported:

- Coefficient ($\beta$)
- HR
- 95% confidence interval (CI) of HR
- p-value of HR

In addition, the following statistics and summary information will be presented for each model overall:

- Sample size (N)
- Number of events of interest
- Number of censored observations
- p-value for Chi square test of overall model fit

### 8.7.5. Missing Values

The proportion of missing data will be reported in descriptive analyses.

This study will not conduct imputation, apart from the following instances:

- Instances of negative number of dispensations (ANTAL) in the dispensation data (i.e. patient returned dispensations) will be matched against (and cancel out) the corresponding dispensation that was initially dispensed at the pharmacy. When matching is not possible, any entries of negative ANTAL will be dropped.

- In instances of missing month of date of death, i.e. date of death is provided as YYYY only, month and day will be set to December 31. In instances of missing day of death, i.e. date of death is provided as YYYY-MM, the date of death will be imputed as the last day of the specified month.

- In instances of missing month of date of birth, used to calculate age at specific points in time, i.e. date of birth is provided as YYYY only, month and day will be set to June 30. In instances of missing day of birth, i.e. date of birth is provided as YYYY-MM, the date of birth will be imputed as the 15$^{th}$ of the specified month.

As the registry data are administrative and reporting is mandatory, there are generally very low levels of missing data. This will be confirmed during the processing of data.

### 8.7.6. Sensitivity Analyses

To test the robustness of the results, the following sensitivity analyses will be performed:

1. Expanding the definition of MACE (Table 10)

2. Utilizing the ITT definition of time at risk, but following patients for a maximum of two years (730 days) after switch and/or discontinuation of study drug, to ensure reasonable temporal proximity between events and the exposure to which events are attributed

3. Changing the end of study date from 31 December 2021 to 31 December 2019, to ensure that any impact of the COVID-19 pandemic on e.g. dispensation patterns or data collection does not alter study findings

For sensitivity analysis 1, the definition of MACE will be based on the expanded list of codes shown in Table 10 below. As in the main analysis, incidence rates will also be estimated for each individual component of this expanded definition of MACE. The rules used to define outcome events described in section 8.3.2 will be applied in this sensitivity analysis as well.

**Table 10: Codes Used in the Definition of MACE in Sensitivity Analysis 1**

| CV event | Type of code | Code |
|---|---|---|
| Unstable angina | ICD-10 | I20.0 |
| Myocardial infarction, including reinfarction | ICD-10 | I21-I22 |
| Stroke (ischemic) | ICD-10 | I63-I64 |
| Transient ischemic attack | ICD-10 | G45 |
| CV death | Codes for underlying cause of death in the CDR, based on ICD-10 | I chapter |

Sensitivity analyses will be performed for both study populations of interest, i.e. for the overall incident user population and for the bio-naïve population, separately. Sensitivity analysis 1 will be performed using both the ITT and and the as-treated definition of exposure time. Sensitivity analyses 2 and 3 will be performed using the primary analysis definition of exposure time (ITT) only. The strata defined in section 8.3.4 will not be analyzed in the sensitivity analyses.

### 8.7.7. Additional analyses

Analyses examining the individual components of MACE (or extended MACE per Sensitivity Analysis 1) will be performed and reported on in the instance that a statistically significant elevated relative risk for ustekinumab is identified in the propensity-score adjusted analysis. In any such instance, a propensity-score adjusted analysis of the individual components of MACE would be conducted specifically based on the exposure definitions, comparators, and subgroups used in the analysis in which the statistically significantly elevated risk is observed.

As previously described, cumulative incidence curves will be generated for each comparator cohort. These will provide insight into the absolute risk of MACE over time for each comparator cohort. In addition to these, IPTW adjusted cumulative incidence curves will be reported, providing insight into the absolute risk of MACE while taking into account differences in patient characteristics between comparator cohorts. For any analysis in which a statistically significant elevated (relative) risk is observed, adjusted survival estimates at 1 year will be reported. In addition, the absolute risk difference between ustekinumab and comparator cohorts will be reported at 24 months of follow up.

The relationship between cumulative dose as well as duration of use of ustekinumab and risk of MACE will not be studied in the main analyses. However, these relationships will be explored by reporting, separately, HRs for 0-1, 0-2, and 0-3 years of follow-up in the as-treated analysis of ustekinumab compared to etanercept.

Since ustekinumab use in the PPD region is not fully captured in the source data to be used in from 2016 and onwards, and as the region makes up around 13% of the total Swedish population, additional baseline patient characteristics will be presented for eligible patients treated with

ustekinumab outside of PPD and for eligible patients treated with ustekinumab in PPD (before 2016), to verify that there are no meaningful differences between these two populations.

## 8.8. Quality Control

The study protocol has been written by following the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct [33] and the Guideline for Good Pharmacoepidemiology Practices (GPP) [34] by the International society for pharmacoepidemiology.

All work will be subject to quality control and documentation procedures to make certain the final report is accurate and thorough, and the analyses can be reproduced. If the data do not permit an analysis as planned or if clarifying analyses are required, the missing or the additional information and results will be included in the report(s) and the corresponding explanation given.

Quality control will also be performed on the retrieved register data, including controlling the inclusion of compulsory variables, such as hospitalization, and main diagnosis, in the delivered register data.

All programs for data management and data analyses will be written by study statistician(s). Quality control check of these programs will be carried out by a statistician other than the one who writes the program. All processes from data management leading to dissemination of study results will undergo quality control checks for programs, result tables and written text.

Secure archives will be maintained for the orderly storage and retrieval of all study related material. An index shall be prepared to identify the archived contents and their locations. Access to the archives will be controlled and limited to authorized personnel only.

## 8.9. Limitations of the Research Methods

The study evaluates diagnosis data from 1 January 2001, the date of first complete coverage of specialist outpatient care data. In some cases, if the actual onset date was before 2001, this will mean that the onset date is set later than the actual onset date. Onset dates are also more likely to be correct for treatment courses starting later in the study period compared to those starting early.

The study does not include primary care data. As such, the date of disease onset is based on first diagnosis in specialist care, and, while not a key consideration in the study, may instead signify the first date of specialist referral. This could also result in under capture of comorbidities (e.g., hypertensive disease, obesity).

As the study uses Swedish data, generalizability of the results may be limited to settings that have similar clinical practices, available treatments, and similar patient characteristics as the Swedish PsO/PsA population.

The study does not make use of prescribers' actual instructions. Instead, patients are assumed to take medication according to the treatment indication/maintenance dosing. This assumption implies that there may be misclassification in outcomes such as compliance with the way in which

patients consume medication depending on prescribers' instructions, which may be related to patients' CV risk.

Infliximab and ustekinumab (in PPD ) are PsO/PsA indicated biologics administered in hospitals and therefore not fully covered by the Swedish Prescribed Drug Registry. Treatment with infliximab, and ustekinumab (in PPD ) are therefore not fully included in this study. Ustekinumab has been administered at hospitals in PPD from 2016 and onwards. While the analysis will censor patients living in PPD at index date (for index dates in 2016 and onwards) to account for this, patients moving to PPD over the study period may be a source of misclassification bias. In addition, patients who have received treatment with infliximab administered in the hospital setting may be misclassified as bio-naïve in the study.

Diagnosis codes are not directly linked to prescribed drugs. Due to the multiple indications for the biologics analyzed in this study, it cannot be certain that patients receive a given biologic for PsO or PsA, even if they are diagnosed as such.

Some patients with PsO alone at index date may go on to develop PsA over the follow-up period. However, while this may affect the risk of MACE it will not affect treatment exposure in the analyses, as the index date, at which point patients are classified as either PsO or PsA patients, is set to the date of treatment initiation.

In analyses of the overall incident user population, patients may have recently been treated with or switched from a different biologic at the point in time from which they are included in an incident user cohort and followed for the outcome of interest. In such cases, particularly those with long prior exposures to a different biologic, the analysis may misattribute events related to the previous exposure to the recently started biologic.

Data on some risk factors relevant for the development of MACE are not available in the data sources to be used and can thus not be fully controlled for. These include e.g. smoking, alcohol use, sedentary lifestyle and level of physical activity. The database also does not capture PsO severity measures. Similarly, while prescribed and dispensed NSAID use will be captured, over the counter NSAID use will not be captured, which will result in some underascertainment of NSAID use. However, since smoking is an important risk factor for CV disease, COPD and nicotine replacement therapies are included as risk factors for the development of MACE as a proxy for the non-available smoking status in this study.

Several study design aspects and analysis methods will be implemented to reduce the potential for bias in the study. The active-comparator incident user design mitigates confounding bias by treatment indication, healthy user, and frailty. The bio-naïve requirement in the primary analysis reduces the risk of misattribution of events related to previous treatment exposures to the exposures under study. In addition, propensity score weighting will be used to improve balance between the ustekinumab and comparator cohorts with respect to a wide number of covariates related to exposure and the outcome of interest. Even so, patients in the registry data are not randomized to therapy. As such, the data are subject to various forms of bias, including treatment selection bias that may not be possible to fully control for.

## 9. PROTECTION OF HUMAN SUBJECTS

The data from the three registries used in this study will be extracted and combined into a research database by the Swedish NBHW. To link patient-level data between the registries, NBHW will identify patients by their individual SSNs. To adhere to patient privacy laws, NBHW will create a unique patient ID number, which is not related to the SSN. Before sending data to Quantify Research, NBHW will remove the SSNs but keep the patient ID number in order to differentiate between patients. This ensures that researchers work with deidentified data only.

The study has been approved by the Swedish national ethical review board and will be conducted in accordance with legal and regulatory requirements and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The study will be conducted in accordance with the EU general data protection regulation 2016/679 (GDPR). The study is based on already collected electronic registry sources and uses pseudo-anonymized data that contain no direct identifiable patient information. Patient consent is not required for registry-based studies such as the one described in this study concept. The study individuals will not be contacted in any phase of the study. Only researchers in the study group will have access to the data to perform statistical calculations and analyses. All study reports will contain aggregate data only and will not identify individual patients. In addition, results will not be reported for subgroups and stratifications including a total of ≤5 patients.

## 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional database study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol. No reporting of individual adverse events to regulatory agencies is planned for this database study because there is no access to individual patient/subject records and it is not possible to assess the causality of individual cases. Pre-specified health outcomes of interest, including any that qualify as adverse events, will be summarized as part of the final study report, which will be provided to regulatory agencies by the sponsor as required.

## 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Patient identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

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# ANNEX 1: STAND-ALONE DOCUMENTS AND ADDITIONAL INFORMATION

## Annex 1.1: List of Stand-alone Documents

**Table 11: National Patient Registry Variable List**

| Variable name | Definition | Value range/categories | Availability |
|---|---|---|---|
| CIVIL (outpatient) | Patient's marital status | G = married<br>OG = not married<br>S = divorced<br>Ä = widow/widower<br>RP = registered partnership<br>SP = separated partnership<br>EP = surviving civil partner | 2001- |
| CIVIL (inpatient) | Patient's marital status | (1997-10 only codes G, O, S, A)<br>G = married<br>OG = not married<br>S = divorced<br>Ä = widow/widower<br>RP = registered partnership<br>SP = separated partnership<br>EP = surviving civil partner | 1997- |
| DIAGNOS (outpatient) | Diagnoses according to ICD10. Max 30 diagnoses | http://www.socialstyrelsen.se/klassificeringochkoder/ | 2001- |
| DIAGNOS (inpatient) | Diagnoses according to ICD10. Max 30 diagnoses | http://www.socialstyrelsen.se/klassificeringochkoder/ | 1964- |
| FODDAT<br>FODDATN<br>(outpatient) | Patient's birth date | Alfanumeric date<br>Numeric date | 2001- |
| FODDAT<br>FODDATN<br>(inpatient) | Patient's birth date | Alfanumeric date<br>Numeric date | 1964- |
| HDIA (outpatient) | Main diagnosis | See ICD-code list:<br>http://www.socialstyrelsen.se/klassificeringochkoder/sokdiagnoskodicd-10-se/ | 2001- |
| HDIA (inpatient) | Main diagnosis | http://www.socialstyrelsen.se/klassificeringochkoder | 1964- |
| INDATUM in (inpatient) | Admission date, expressed as number of days from 1960-01-01 until admission. | Numeric date | 1964- |

| Variable name | Definition | Value range/categories | Availability |
|---|---|---|---|
| INDATUMA in (inpatient) | Date of admission | Alfanumeric date | 1964- |
| KON (outpatient) | Patient's gender | 1=man 2=woman | 2001- |
| KON (inpatient) | Patient's gender | 1=man 2=woman | 1964- |
| UTDATUM i n (inpatient) | Date of discharge | Numeric date | 1964- |
| UTDATUMA in (inpatient) | Date of discharge | Alfanumeric date | 1964- |

**Table 12: Prescribed Drug Registry Variable List**

| Variable name | Definition | Value range/categories | Availability | Missingness | Information concerning |
|---|---|---|---|---|---|
| ATC | ATC code according to WHO. ATC codes classify drugs by organ/system of usage and chemical properties. | | 2005-07-01 | ~0% | Product |
| ANTAL | Number of packages dispensed. Can be a decimal number if the drug is dose dispensed. Negative values occur if entries have been corrected, which is done by addition of a new row with a negative value of the corresponding dispensation. | | 2005-07-01 | No | Prescription |
| EDATUM | Dispensation date. Date when the patient purchased the product. | Numeric date | 2005-07-01 | No | Prescription |
| FDATUM | Prescription date. Date when the | Numeric date | 2005-07-01 | No | Prescription |

| Variable name | Definition | Value range/categories | Availability | Missingness | Information concerning |
|---|---|---|---|---|---|
| | product was prescribed. | | | | |
| ANTNUM | Pack size (numeric, no unit). Information about pack size for special permission (license) drugs is missing since fall 2013. | | 2005-07-01 | | Product |
| LK | Patient's place of residence at the time of dispensation. County and municipality. | PPD | 2005-07-01 | | Patient |

| Variable name | Definition | Value range/categories | Availability | Missingness | Information concerning |
|---|---|---|---|---|---|
| | | PPD | | | |
| STYRKALF | Strength of the product (alphanumeric). | E.g. 5 mg, 9mg/mL or 2% | 2005-07-01 | | Product |
| STYRKNUM | Strength of the product (numeric, no unit). | | 2005-07-01 | | Product |

**Table 13: Cause of Death Registry Variable List**

| Variable name | Definition | Value range/categories | Availability | Missingness |
|---|---|---|---|---|
| DODSDAT | Date of death | Alfanumeric date | 1952- | 1952-1960 only has year and month. |
| DODSDATN | Date of death | Numeric date | 1961- | About 1-2% since 1979 |

**Table 14: Charlson Comorbidity Index Code List** [a]

| Comorbidity | ICD-10 diagnosis codes | Weight |
|---|---|---|
| Myocardial infarction | I21.x, I22.x, I25.2 | 0 |
| Congestive heart failure | I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, P29.0 | 2 |
| Peripheral vascular disease | I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9 | 0 |
| Cerebrovascular disease | G45.x, G46.x, H34.0, I60.x –I69.x | 0 |
| Dementia | F00.x–F03.x, F05.1, G30.x, G31.1 | 2 |
| Chronic pulmonary disease | I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3 | 1 |
| Rheumatologic disease | M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0 | 1 |
| Peptic ulcer disease | K25.x–K28.x | 0 |

[a] Quan, H., Li, B., Couris, C. M., et al., Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. American journal of epidemiology, 2011. 173(6): p. 676-682.

| Comorbidity | ICD-10 diagnosis codes | Weight |
|---|---|---|
| Mild liver disease | B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4 | 2 |
| Diabetes without chronic complications | E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 | 0 |
| Diabetes with chronic complications | E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7 | 1 |
| Hemiplegia or paraplegia | G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9 | 2 |
| Renal disease | I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2 | 1 |
| Any malignancy, including leukemia and lymphoma | C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x | 2 |
| Moderate to severe liver disease | I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7 | 4 |
| Metastatic solid tumor | C77.x–C80.x | 6 |
| AIDS/HIV | B20.x–B22.x, B24.x | 4 |
| Maximum comorbidity score | | 24 |

## ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

| Section 1: Research question | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 1.1 Does the formulation of the research question clearly explain: | | | | |
| 1.1.1 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) | ☒ | ☐ | ☐ | 6.2 |
| 1.1.2 The objectives of the study? | ☒ | ☐ | ☐ | 7 |
| 1.2 Does the formulation of the research question specify: | | | | |
| 1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized) | ☒ | ☐ | ☐ | 8.2.1 |
| 1.2.2 Which formal hypothesis(-es) is (are) to be tested? | ☒ | ☐ | ☐ | 7 |
| 1.2.3 if applicable, that there is no a priori hypothesis? | ☐ | ☐ | ☒ | |

| Section 2: Source and study populations | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 2.1 Is the source population described? | ☒ | ☐ | ☐ | 8.2.1 |
| 2.2 Is the planned study population defined in terms of: | | | | |
| 2.2.1 Study time period? | ☒ | ☐ | ☐ | |
| 2.2.2 Age and sex? | ☒ | ☐ | ☐ | |
| 2.2.3 Country of origin? | ☒ | ☐ | ☐ | 8.2 |
| 2.2.4 Disease/indication? | ☒ | ☐ | ☐ | |
| 2.2.5 Co-morbidity? | ☒ | ☐ | ☐ | |
| 2.2.6 Seasonality? | ☐ | ☐ | ☒ | |
| 2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 8.2 |

Comments: None

| Section 3: Study design | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | 8.3.2 |
| 3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design) | ☒ | ☐ | ☐ | 8.1.1 |
| 3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 8.7.3 |
| 3.4 Is sample size considered? | ☒ | ☐ | ☐ | 8.5 |
| 3.5 Is statistical power calculated? | ☒ | ☐ | ☐ | |

Comments: None

| **Section 4: Data sources** | **Yes** | **No** | **N/A** | **Section Number(s)** |
|---|---|---|---|---|
| 4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc) | ☒ | ☐ | ☐ | |
| 4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc) | ☒ | ☐ | ☐ | 8.4 |
| 4.1.3 Covariates? | ☒ | ☐ | ☐ | |
| 4.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 8.3.1 |
| 4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 8.3.2 |
| 4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.) | ☒ | ☐ | ☐ | 8.3.3 |
| 4.3 Is the coding system described for: | | | | |
| 4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) | ☒ | ☐ | ☐ | 8.3.3 |
| 4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) | ☒ | ☐ | ☐ | 8.3.2 |
| 4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) | ☒ | ☐ | ☐ | 8.3.1 |
| 4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 8.1.2 |

Comments: None

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number(s)** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure) | ☒ | ☐ | ☐ | 8.3.1 |
| 5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study) | ☒ | ☐ | ☐ | 8.4 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 8.3.1 |
| 5.4 Is exposure classified based on biological mechanism of action? | ☐ | ☒ | ☐ | |
| 5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☒ | ☐ | ☐ | 8.3.1, 8.7.7 |

Comments: Exposure is defined on an individual drug-level

| Section 6: Endpoint definition and measurement | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 6.1 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | 8.3.2 |
| 6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 8.4 |

Comments: None

| Section 7: Biases and Effect modifiers | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 7.1 Does the protocol address:<br>7.1.1 Selection biases? | ☒ | ☐ | ☐ | 8.7.2, 8.9 |
| 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | |
| 7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders) | ☒ | ☐ | ☐ | 8.7.2.1 |
| 7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect) | ☒ | ☐ | ☐ | 8.3.4 |
| 7.4 Does the protocol address other limitations? | ☒ | ☐ | ☐ | 8.9 |

Comments: Analyses will be stratified based on potential effect modifiers of interest, as outlined in Section 8.3.4.

| Section 8: Analysis plan | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 8.1 Does the plan include measurement of absolute effects? | ☒ | ☐ | ☐ | 8.7.3, 8.7.7 |
| 8.2 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 8.7.4 |
| 8.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 8.7.1 |
| 8.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 8.3.4 |
| 8.5 Does the plan describe the methods for identifying:<br>8.5.1 Confounders?<br>8.5.2 Effect modifiers? | ☒<br>☐ | ☐<br>☒ | ☐<br>☐ | 8.7.2.1 |
| 8.6 Does the plan describe how the analysis will address:<br>8.6.1 Confounding?<br>8.6.2 Effect modification? | ☒<br>☐ | ☐<br>☒ | ☐<br>☐ | 8.7 |

Comments: Analyses will be stratified based on potential effect modifiers of interest, as outlined in Section 8.3.4

| Section 9: Quality assurance, feasibility and reporting | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 8.8 |
| 9.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 8.8 |
| 9.3 Does the protocol describe quality issues related to the data source(s)? | ☒ | ☐ | ☐ | 8.4, 8.7.5, 8.9 |
| 9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 8.5 |
| 9.5 Does the protocol specify timelines for | | | | |
| 9.5.1 Start of data collection? | ☒ | ☐ | ☐ | 5 |
| 9.5.2 Any progress report? | ☐ | ☒ | ☐ | 5 |
| 9.5.3 End of data collection? | ☒ | ☐ | ☐ | 5 |
| 9.5.4 Reporting? (i.e. interim reports, final study report) | ☒ | ☐ | ☐ | 5 |
| 9.6 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | 3 |
| 9.7 Are communication methods to disseminate results described? | ☒ | ☐ | ☐ | 11 |
| 9.8 Is there a system in place for independent review of study results? | ☐ | ☒ | ☐ | |

Comments: Progress reports are not planned for the study.

| Section 10: Ethical issues | Yes | No | N/A | Section Number(s) |
|---|---|---|---|---|
| 10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described? | ☒ | ☐ | ☐ | 9 |
| 10.2 Has any outcome of an ethical review procedure been addressed? | ☒ | ☐ | ☐ | 9 |
| 10.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 9 |

Comments: None

## PARTICIPATING PHYSICIAN AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

**Principal Participating Physician:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

**Sponsor's Responsible Medical Officer (Main Author):**

Name (typed or printed): PPD

Institution: Johnson & Johnson PPD

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

**Note:** If the address or telephone number of the participating physician changes during the course of the study, written notification will be provided to the sponsor; a protocol amendment will not be required.

# Signature

| User | Date | Reason |
|---|---|---|
| PPD | 06-Mar-2023 15:17:00 (GMT) | Document Approval |
| Oster-Gozet Laurence PPD | 07-Mar-2023 10:56:13 (GMT) | Document Approval |