1. ABSTRACT

Name of Sponsor/Company	**Janssen-Cilag International NV**
Name of Finished Product	STELARA®
Name of Active Ingredient(s)	Ustekinumab

Protocol No.: PCSIMM004697

Title of Study: 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
(Version 0.7, 31 March 2023)

Study Name: Quantify STELARA MACE Study

Sponsor's Responsible Party: PPD

Keywords: MACE, Biologics, Psoriasis, Psoriatic Arthritis, RWE

EU PAS Register Number: EUPAS49873

NCT No.: N/A

Clinical Registry No.: N/A

Marketing Authorization Holder(s): Janssen-Cilag International NV

Names and Affiliations of Principal Investigator: PPD

Study Country: Sweden

Publication (Reference): None.

Study Period: 1 July 2009 to 31 December 2021

Background and Rationale:

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 MAH proposed to perform additional analyses in 2 studies (in the response to RSI), and in the assessment the EMA/PRAC requested to include these as 2 additional post-authorization safety studies (PASS's) in the European Risk Management Plan (EU-RMP) to expand the evidence base on the risk of major adverse cardiovascular events (MACE) associated with ustekinumab in patients with psoriasis and psoriatic arthritis (PsA). The purpose of this study was to aid in addressing the risk of MACE in psoriasis and PsA patients treated with ustekinumab.

Research Question and Objectives:

The primary objective was to estimate and compare the risk of MACE (composite outcome of myocardial infarction, ischemic stroke, and cardiovascular death) in psoriasis and PsA patients initiating treatment with ustekinumab (L04AC05) relative to patients initiating treatment with etanercept in routine clinical practice in Sweden. The secondary objectives were to estimate the risk compared to treatment with adalimumab and secukinumab, and to compare the risk also between the comparators.

Study Design:

This was an observational, non-interventional database study, based on secondary use of patient-level data from Swedish population-based national registers, using an active-comparator, new-user design. The study population of interest was adult psoriasis and PsA patients diagnosed in secondary care between 2001-2021, initiating treatment with ustekinumab or another biologic of interest (i.e., etanercept, adalimumab, secukinumab) during the study inclusion period (1 July 2009 to 30 December 2021).

Patients were allocated to mutually exclusive incident user cohorts based on the first study drug initiated during the study inclusion period. The new-user treatment cohorts were analyzed in the context of two populations: 1) the bio-naïve population, including patients initiating a treatment with a cohort-defining biologic who had not been previously treated with any psoriasis/PsA indicated biologic or Janus kinase (JAK)-inhibitor, and 2) the overall incident user population, including patients initiating treatment with a cohort-defining biologic who may or may not have previously been treated with another biologic/JAK inhibitor.

Setting:

This non-interventional database study was based on secondary use of patient-level data from Swedish population-based national registers. The data sources for the study were Swedish, national, population-based registers (National Patient Registry, Prescribed Drug Registry, Cause of Death Registry and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies). Data for all patients with a primary psoriasis and/or PsA diagnosis recorded between 1 January 2001 and 30 December 2021 in specialist care in Sweden were extracted from registers held by the Swedish National Board of Health and Welfare (NBHW) and Statistics Sweden.

Patient Population and Study Size:

Patients were considered eligible for inclusion if they were at least 18 years at the index date (first initiation of treatment), had a confirmed primary diagnosis of psoriasis/PsA recorded between 1 January 2001 and 30 December 2021 (prior to initiation of cohort-defining treatment), initiated treatment with one of the cohort-defining biologics during the inclusion period (1 July 2009 to 30 December 2021) and had lived in Sweden for at least 5 years at time of the index date. The projected number of patients to be analyzed in the primary objective, comparing ustekinumab to etanercept, using the primary analysis definitions was ~580 bio-naïve ustekinumab initiators and ~5400 bio-naïve etanercept initiators. These projections were 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), together with publicly available data from the NBHW on the total number of patients with dispensations of the study drugs of interest.

Variables and Data Sources:

Demographics and baseline characteristics such as age, sex, time since disease onset, educational level, disease history and prior treatment history, were defined based on information available in the registers from either NBHW or Statistics Sweden.

The outcome (MACE) was defined based on any of cardiovascular death, ischemic stroke (IS), and/or myocardial infarction (MI), all of which were defined using ICD10 codes available in the Patient Register (in- and outpatient visits) and in the Cause of Death Register. Time at risk was defined as time from initiation of treatment until an event (MACE), (non-CV) death, emigration, end of data availability (for ITT definition), or discontinuation or switching to another biologic/JAK inhibitor (for as-treated definition), whichever came first.

Statistical Methods:

In the primary analysis, an intention-to-treat (ITT) exposure definition was used. As such, patients were 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 came first. In the secondary analysis, an as-treated exposure definition was used; patients were thus followed from first initiation of treatment with a study drug during the study inclusion period until MACE, death, switch to another biologic/JAK inhibitor, discontinuation of the cohort-defining biologic, emigration, or end of data availability, whichever came first.

Risk of MACE was analyzed using cumulative incidence estimation and incidence rates for unadjusted risk, estimated for each treatment cohort. Cox proportional hazards regression with stabilized inverse probability of treatment weighting by propensity scores was used to adjust for confounding by treatment selection. The propensity score was 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.

RESULTS:

PARTICIPANTS AND PATIENT CHARACTERISTICS: A total of 15,502 patients were included after exclusions, of which 13,086 were considered bio-naïve. Of these 13,086 bio-naïve patients, 525 and 4,888 were treated with ustekinumab and etanercept, respectively, which was slightly lower than expected. However, follow-up was longer (average 5.0 and 5.4 years) compared to the 3 and 4 years used in the power calculation. The remaining bio-naïve patients were those who had initiated treatment with either adalimumab (n=7204) or secukinumab (n=469).

The mean age of the bio-naïve population was similar across treatment cohorts, ranging from 49.3±14.4 (mean ± SD) in the adalimumab cohort, to 50.5±14.0 years in the etanercept cohort. The proportion of female patients was lower in the ustekinumab cohort (38.3%) compared with the etanercept (51.1%), adalimumab (46.3%) and secukinumab (45.8%) cohorts. The ustekinumab cohort also had fewer patients with PsA, a higher proportion of patients with PsO, and a higher proportion of patients with inflammatory bowel disease, compared to the other treatment cohorts. A larger proportion of the patients in the ustekinumab cohort were bio-experienced (38.4%) compared to the etanercept cohort (12.1%), most of which were due to prior use of TNF inhibitors. Other characteristics were more similar between cohorts, including prevalence of cardiovascular comorbidities and risk factors such as obesity, diabetes, hypertension, dyslipidemia and history of MACE. As the bio-naïve population accounted for 84% of the overall incident user population, similar characteristics were present in the incident user cohorts.

OUTCOME DATA: Over the entire follow-up period (maximum 12.5 years) using the ITT exposure definition, there was a total of 397 MACE events in the bio-naïve population (ustekinumab cohort: n=21; etanercept cohort: n=191; adalimumab cohort: n=172; secukinumab cohort: n=13) , and 510 MACE events in the overall incident user population (ustekinumab cohort: n=35; etanercept cohort: n=224; adalimumab cohort: n=231; secukinumab cohort: n=20).

MAIN RESULTS: In the main analysis, i.e., of bio-naïve initiators and using the ITT exposure definition, the mean (SD) duration of follow-up was 5.0 (3.1) and 5.4 (3.0) for the ustekinumab and etanercept cohorts, respectively, with unadjusted incidence rates for MACE of 0.79 (95% CI: 0.52 – 1.22) per 100PY and 0.72 (95% CI: 0.63 – 0.83) per 100PY, respectively. The unadjusted cumulative incidence of MACE at 5 years was 4.11% (95% CI: 2.42 – 6.48) and 3.57% (95% CI: 3.00 – 4.21) in the ustekinumab and etanercept cohorts, respectively. The IPTW-adjusted analyses of MACE revealed no statistically significant increased risk of MACE when comparing patients in the ustekinumab cohort to those in the etanercept cohort (HR=1.04, 95% CI: 0.40-2.70).

The unadjusted incidence rates and cumulative incidences in the overall incident user population were also similar between the ustekinumab and etanercept cohorts. The incidence rates of MACE were 0.77 (95% CI: 0.56 – 1.08) per 100PY and 0.73 (95% CI: 0.64 – 0.83) per 100PY for the ustekinumab and etanercept cohorts, respectively. At 5 years, the unadjusted cumulative incidences for MACE were 3.60% (95% CI: 2.36 – 5.24) in the ustekinumab cohort and 3.63 (95% CI: 3.10 – 4.22) in the etanercept cohort. Again, the IPTW-adjusted analyses of MACE revealed no statistically significant increased risk of MACE (HR=0.81, 95% CI: 0.44-1.50).

In addition, there were no statistically significant HRs for ustekinumab versus etanercept when restricting the analyses to any of the subgroups (psoriasis alone, psoriasis with/without PsA, PsA with/without psoriasis, high CV risk, low CV risk, broadened MACE definition, 2-year cap on the ITT exposure time definition, study end by 2019), either in the bio-naïve population or the overall incident user population. In general, HRs were <1 when comparing ustekinumab to etanercept.

RESULTS ADDRESSING SECONDARY OBJECTIVES: The IPTW-adjusted analyses addressing the secondary objectives revealed no statistically significant increased risk of MACE when comparing the ustekinumab and adalimumab cohorts. Estimates were in general <1, and the hazard ratio was statistically significantly lower for the ustekinumab cohort compared to the adalimumab cohort in the bio-naïve population using the ITT exposure time definition for the following stratifications and sensitivity analyses: PsA with/without psoriasis (HR=0.31, 95% CI: 0.12-0.84), 2-year cap on the ITT exposure time definition (HR=0.48, 95% CI: 0.24, 0.97), and study end by 2019 (HR=0.43, 95% CI: 0.21-0.89). When comparing the ustekinumab cohort to the secukinumab cohort, the HRs were in general >1, although there were no statistically significant HRs except for the sensitivity analysis of the bio-naïve population using the ITT exposure time definition and the broad MACE definition (HR=2.44, 95% CI: 1.15-5.15). For the remaining comparisons in the secondary objective (adalimumab vs. etanercept and secukinumab vs. etanercept), there were no statistically significant HRs in any analysis and the HRs were in general close to 1 for the adalimumab-etanercept comparisons and >1 for the secukinumab-etanercept comparisons.

DISCUSSION AND CONCLUSION:

DISCUSSION: The present study revealed no increased risk of MACE associated with initiation of ustekinumab vs. initiation of TNF inhibitors, which held true across all pre-specified stratifications and sensitivity analyses, regardless of the population studied (bio-naïve or overall incident users) and the exposure time definition used (ITT or as-treated). While a statistically significantly elevated risk was observed when comparing the ustekinumab cohort to the secukinumab cohort among the bio-naïve initiators in the sensitivity analysis expanding the definition of MACE using the ITT exposure time definition, this was not the case in the corresponding overall incident user analysis, in which the sample size was increased by >60%, using either the ITT or the as-treated exposure time definition, nor in the corresponding bio-naïve analysis using the as-treated exposure time definition.

CONCLUSIONS: In conclusion, in this study of psoriasis and PsA patients in Sweden spanning more than ten years and with nationwide coverage, the observed results indicate no increased risk of major cardiovascular events for ustekinumab compared with etanercept, adalimumab and secukinumab in a real-world setting.