4.0   Abstract

Title:

A Post-Marketing Registry-Based Prospective Cohort Study of Long-Term Safety of Risankizumab in Denmark and Sweden

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Rationale and Background:

Psoriasis is a chronic, relapsing inflammatory disease of the skin. Targeted biological therapies have become established treatments of psoriasis. These biologicals are designed to block specific molecular steps important in the pathogenesis of the disease. Risankizumab (Skyrizi[TM], Abbvie) was approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in April 2019 for the treatment of individuals with moderate to severe plaque psoriasis, who are candidates for systemic therapy. Risankizumab is a humanized IgG1 monoclonal antibody that selectively inhibits interleukin (IL)-23 by specifically targeting the p19 subunit. Although the risankizumab clinical trials provide valuable information on the product's efficacy and safety, long-term safety data are needed for individuals who are exposed to risankizumab. A prospective population-based cohort study of individuals in routine clinical practice will be conducted to investigate the incidence and occurrence of safety outcomes such as malignancies, major adverse cardiovascular events (MACE), and serious infections. In addition, the incidence and occurrence of serious hypersensitivity reactions and incident hepatitis B and C, will be explored. The PAS study is a commitment to the EMA and FDA.

Research Question and Objectives:

The aim of the study is to estimate the risk of malignancy, MACE, serious infections, serious hypersensitivity reactions and incident hepatitis B and C among individuals with psoriasis who were exposed to risankizumab, relative to individuals with psoriasis

exposed to other systemic treatments (biologics and non-biologics) divided into three subgroups, other IL-inhibitors treatment (excluding risankizumab), TNF-α inhibitor treatment, and non-biologic systemic treatment.

The objectives are to estimate the risk of the following events in individuals with psoriasis exposed to risankizumab relative to individuals with psoriasis exposed to other systemic psoriasis treatments:

- overall malignancy excluding NMSC
- NMSC
- MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death)
- serious infections (incl. opportunistic infections)
- serious hypersensitivity reactions
- incident acute and chronic hepatitis B
- incident acute and chronic hepatitis C.

Study Design:

The study is a non-interventional, population-based, register-based cohort study of individuals with psoriasis identified in the Danish and Swedish nationwide registers. An active-comparator, new user study design will be used to assess the association between the use of risankizumab and the outcomes of interest.

Population:

The study population consists of all individuals with a recorded diagnosis of psoriasis or psoriasis arthritis in the national patient registers and with at least one dispensed prescription of a biological or a non-biological drug used for systemic treatment of psoriasis recorded in the national prescribed drug registers.

Variables:

The main exposure of interest will be use of risankizumab. Active comparator subgroups will be (i) other IL-inhibitors (excluding risankizumab), (ii) TNF-α inhibitors, and (iii) non-biological systemic treatment. The study outcomes will be malignancies, MACE, serious infections, serious hypersensitivity reactions and incident hepatitis B and C. Incident malignancy will be identified via the linked national cancer registers in each country. The other outcomes will be captured through inpatient and specialist outpatient diagnoses in the patient registers. Covariates such as comorbidities and previous and concomitant drug therapies will be retrieved from hospital diagnoses and dispensed prescriptions. Information on age, sex, region of residency, and education will be retrieved from the population registers. For those individuals in the study population that are also registered in the specialized psoriasis registers information about BMI, smoking, and alcohol intake will be obtained.

Data Sources:

Linked data from the national health and population registers in Denmark and Sweden. Data from the specialized psoriasis registers in both countries will also be linked to the other data sources.

Study Size:

The study will include all individuals fulfilling the inclusion criteria. Since risankizumab is anticipated to enter the market in Europe during 2019, and the uptake of the drug is unknown, it is not possible to estimate the study size. The sample size is estimated based on the desired precision of the effect measures, assuming 95% confidence, incidence rate of the outcome malignancy excluding NMSC in the comparator treatment group being 0.68 per 100 person-years, a 1:2 ratio of risankizumab to comparator person-years, and a rate ratio of 1.6, 2.0, 2.5, and 3.0 for risankizumab versus risankizumab unexposed biologic and non-biologic comparators. Outcome analyses will be performed when the

data will capture at least 5,000 person-years of exposure to risankizumab, which will rule out a rate ratio of 2.0 for risankizumab versus comparators.

Data Analysis:

Appropriate statistical analyses in an active-comparator design will be used. Cox proportional hazards model will be used to calculate hazard ratios. Propensity score matching will be used to adjust for confounding.

Milestones:

AbbVie will initiate the study upon endorsement of the study protocol by the EMA and FDA. Study progress will be reported every year starting from 2022 to 2034. An extended study progress report will be submitted to the EMA and to the FDA in Q3 2023. Interim reports of study results will be submitted to the EMA in December 2026 and in December 2030, and the final study report will be submitted to the EMA and to the FDA in December 2034.

Investigators:

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