NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: An Active Surveillance, Post-Authorization Safety Study (PASS) to Estimate Incidence Rates of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) within the German Registry Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)

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Keywords: Rheumatoid arthritis, cohort study, rituximab, serious infection, malignancy, cardiovascular disease

Rationale and background: Approved in the European Union (EU) on 01 April 2020, PF-05280586 (Ruxience) was developed by Pfizer as a biosimilar to the licensed reference product, MabThera. Pfizer proposed the assessment of safety events of special interest based on the Ruxience EU Risk Management Plan (RMP) version 1.0 ((infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on cardiovascular disease (CVD) (Important Potential Risk) and use in pregnancy (Missing Information)).[1] This study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer as a "Category 4 Additional Pharmacovigilance Activities" in line with the reference product.

Research question: What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis (RA) who are enrolled in the RABBIT register and initiate treatment with Ruxience?

Objectives: To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and use during pregnancy among all patients with RA in the RABBIT register who initiate Ruxience.

Study design: This is an active surveillance study using existing data within the German register Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT), an ongoing prospective observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketing clinical use. This final report includes therapy and safety data from patients with RA enrolled and observed in the RABBIT register from the first Ruxience initiator in 2020 until 31 December 2023.

Setting: The setting of the study was the RABBIT register.

Patients and study size, including dropouts: The study population was comprised of all patients with RA enrolled at an age of at least 18 years within the RABBIT register (who

[1] Ruxience (rituximab) European Union Risk Management Plan Version 1.0 dated December 2019. ruxience-epar-risk-management-plan-summary_en.pdf (europa.eu)

were diagnosed with RA with an minimum age of at least 16 years) who initiated treatment with Ruxience beginning with the first Ruxience initiator through 31 December 2023.

Variables and data sources: Safety events of special interest were primarily based on the safety events in the Ruxience risk management plan The following safety events of interest were defined a priori and investigated in the final report:

- Hospitalised infections overall.
- Serious cardiac disorders: heart failure, coronary artery disease, myocardial infarction, other cardiac disorders.
- Malignancies, excluding non-melanoma skin cancer (NMSC).
- NMSC.
- Events associated with use during pregnancy.

Crude, unadjusted incidence rates of pre-defined safety events of interest were calculated per 1,000 patient years. The results were based on the on-drug approach with a three-month risk window. Additionally, malignancy outcomes were analysed with a once-exposed always at risk (ever-exposed) approach and an ever-exposed approach including a 180-day induction period after treatment initiation (time at risk started 180 days after treatment initiation).

Results: From the time of initiation of Ruxience in 2020 until 31 December 2023, 19 patients initiated treatment with Ruxience either at enrolment (n=1) or during follow-up (n=18) and were therefore eligible for this analysis. These patients had a mean total follow-up time in the RABBIT register of 5 years and a mean duration of Ruxience exposure of 8.9 months. The total exposure time amounted to 14.8 PY in the on-drug approach adding a three-month risk window, 38.0 PY in the ever-exposed approach without induction period, and 28.8 PY in the ever-exposed approach considering an induction period. At the time of Ruxience initiation, patients were on average 65 years old, and 68% were female.

During the time of observation, one event of hospitalised infection, (incidence rate (IR) 67.8 (95% confidence interval (CI) 1.72-377.74) per 1,000 person years (PY), two events of serious cardiac disorders (IR 136.4 (95% CI 16.51-492.48) per 1,000 PY) and no events for the outcomes malignancies and non-melanoma skin cancer under treatment with Ruxience. Further, there were no patients exposed to Ruxience prior to or during pregnancy.

Discussion:. During the period of observation, the uptake of Ruxience among patients with RA in the RABBIT register was very low (n=19). This resulted in a low number of patient years, and few or no reported safety events of special interest in patients exposed to Ruxience. Due to the limited uptake of Ruxience in the RABBIT register, no conclusions can be drawn from these data.

Marketing Authorization Holder(s): Pfizer, Inc

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