# 4.0 Abstract

**Title:**

Long-term comparative safety cohort studies of upadacitinib (Rinvoq™) use for the treatment of RA in Europe

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**Rationale and Background:**

Upadacitinib (Rinvoq™) is a selective and reversible inhibitor of Janus Kinase-1 (JAK1) approved in Europe on 16 December 2019 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Upadacitinib may be used as monotherapy or in combination with methotrexate (MTX) or other conventional synthetic DMARDs (csDMARDs). Although the upadacitinib clinical trials provide valuable information on the product's efficacy and safety, assessment of long-term safety using randomized clinical trial (RCT) data is limited due to the size and extent of long-term data. Long-term safety data are needed in patients in routine clinical practice who are exposed to upadacitinib (Rinvoq™), including patients not included or subgroups of patients for whom there is limited data in the clinical program. Using data derived from European RA registries, this study aims to evaluate the long-term safety of upadacitinib relative to other approved therapies for the treatment of RA.

**Research Question and Objectives:**

The purpose of this study is to evaluate and characterise the important identified and potential risks of upadacitinib (Rinvoq™) and missing information on the safety of upadacitinib, as described in the European Union (EU) Risk Management Plan (RMP) for Rinvoq™ (upadacitinib). This study aims to evaluate the long-term safety of upadacitinib among patients with RA receiving routine clinical care. The primary objective is to describe and compare (when possible) the incidence rates of the following important risks

as described in the EU RMP for Rinvoq™ (upadacitinib) among upadacitinib-treated patients with RA and similar patients treated with other approved therapies indicated for the treatment of RA (e.g., csDMARDs, biologic DMARDs [bDMARDs]; excluding other JAK inhibitors): serious and opportunistic infections (including herpes zoster and tuberculosis [TB]), malignancies, major adverse cardiovascular events (MACE), venous thromboembolism (VTE), mortality, gastrointestinal (GI) perforations, and liver injury (including drug-induced liver injury [DILI]). The secondary objective is to describe the incidence rates among patients with missing information on the safety of upadacitinib, including the very elderly (≥ 75 years of age), and when data are available, in patients with moderate hepatic impairment, patients with severe renal impairment, and patients with evidence of chronic infection with hepatitis B or hepatitis C.

**Study Design:**

Prospective population-based cohort studies of patients in the real-world will be conducted utilising European RA registries to monitor the incidence of safety outcomes among patients exposed to upadacitinib (Rinvoq™) for the treatment of RA compared to patients exposed to selected standard of care comparator RA treatments. A new user, active comparator cohort study design will be used to estimate rates of events of interest in patients treated with upadacitinib (Rinvoq™) and in patients treated with comparator (i.e., non-JAK inhibitor standard of care) therapies. The study will include up to 3 – 5 years of patient accrual (for malignancy) with up to 8 years of patient follow-up in total for the first patient enrolled, when possible. A study period of up to 8 years will allow evaluation of longer latency outcomes, including malignancy.

**Population:**

This study includes patients diagnosed with RA and identified from one of five European clinical RA registries in Sweden, Denmark, the UK, Spain, and Germany.

**Variables:**

Exposure:

Each registry assigns drug exposure time to an exposure cohort based on medication classification (Table 2). Exposure is reported by the physician at enrolment into each registry; however, cohort definitions vary across the registries (Table 3). Changes to exposure are reported by the physician at follow-up visits. In ARTIS, registry data are combined with data on prescription medication from national registries to assign exposure.

For all registries, the upadacitinib cohort will include patients with RA initiating treatment with upadacitinib. The comparator cohorts will include the following:

ARTIS and DANBIO (Sweden and Denmark):

- *bDMARD cohort:* Patients with RA initiating a bDMARD treatment (can be stratified into patients initiating their first, second, and third biologic)
- *Biologic naïve cohort:* Patients with RA without concurrent use or history of bDMARDs or tsDMARDs
- *Matched general population cohort:* People without RA are identified via population registers and matched with DANBIO and ARTIS patients

BSRBR-RA (United Kingdom):

- *Anti-TNFα cohort:* Patients with RA initiating anti-TNFα therapy (defined as originator etanercept, infliximab or adalimumab only and biologic naïve at registration). This is a specified cohort designed for the purpose of comparison with newer agents.
- *Biologic naïve DMARD cohort:* Patients with RA having active RA (DAS28 > 4.2) despite current treatment with a csDMARD; new use of a non-biologic DMARD is not required for comparator patients

BIOBADASER (Spain):

- *bDMARD cohort*: Patients with RA initiating a bDMARD treatment

RABBIT (Germany):

- *bDMARD cohort:* Patients with RA initiating a bDMARD treatment (can be stratified into patients initiating their first, second, and third biologic)
- *Biologic naïve DMARD cohort:* Patients with RA initiating a csDMARD treatment (without concomitant biological therapy) after failure of at least one csDMARD treatment and without prior exposure to bDMARDs or tsDMARDs

Outcomes:

Each registry collects a series of safety outcomes that reflect registry objectives and correspond to safety events of interest in this AbbVie study (Table 4). The important safety events in this protocol include malignancies (including NMSC), serious and opportunistic infections (including herpes zoster and TB), MACE, VTE, mortality, GI perforations, and acute liver injury (including DILI). In ARTIS and DANBIO, outcomes are identified by linkages with several national registries. For BSRBR-RA, BIOBADASER, and RABBIT, outcomes are obtained by physician reports (an exception in BSRBR-RA is cancer and death outcomes that are additionally confirmed via linkages with National Health Service [NHS] Digital and in RABBIT deaths (and causes of deaths) are confirmed with national authorities).

Covariates:

Each RA registry collects detailed patient information on RA disease severity, concomitant medication use, and comorbidities.

**Data Sources:**

Data for this study will be obtained from five RA patient registries (ARTIS, DANBIO, BSRBR-RA, BIOBADASER, and RABBIT) as well as Nordic nationwide health

registers. These registries provide high-quality, longitudinal data capture of adult patients being treated with approved anti-rheumatic treatments.

**Study Size:**

The number of patients in the upadacitinib and comparator cohorts, the duration of patient follow-up, and the power to detect differences in risk between the cohorts will vary between the registries. The final study size will depend on the total eligible patients included within each RA Registry during the study period. Each in Denmark and Sweden, a cohort of at least 2,000 upadacitinib-exposed patients and at least 2,000 in each comparator cohort (bDMARD/anti-TNFα cohort and biologic naïve cohorts) with a mean length of follow-up of 6 years for malignancy and 2.5 years for shorter latency outcomes is targeted. This will provide adequate power (80%) to detect at least a hazard ratio (HR) of 1.5 after completion for malignancies including nonmelanoma (squamous cell) skin cancer, MACE, mortality, and serious infections. In the remaining RA registries, as many upadacitinib-exposed patients as possible will be included in the study to provide descriptive data complimentary to DANBIO and ARTIS.

**Data Analysis:**

Analyses will be conducted separately for each outcome in each registry and will include descriptive analyses of baseline characteristics and cumulative rates of study endpoints (i.e., events of special interest or serious adverse events [SAEs], depending on registry) for each exposure cohort. Comparative analyses will be performed to evaluate whether upadacitinib treatment is associated with an increased risk of outcomes of interest relative to control cohorts. If available and appropriate, registry-specific unadjusted results (and adjusted results when a common statistical model is used) may be pooled across additional registries for selected outcomes.

ARTIS and DANBIO: Descriptive analyses will include baseline patient information and incidence rates of events of special interest for each exposure cohort. Comparative analyses will be performed using Cox regression with multivariable adjustment to address

imbalances among potential confounding factors across the comparison groups that may confound the association between exposure and outcomes. Registry-specific overall and stratified risks ratios for each outcome will be pooled using meta-analytic techniques. ARTIS and DANBIO registry-specific risk ratios will also be compared with an age- and sex-matched general population comparator cohort in each country via linkage to the national population and patients registers to attain standardised incidence ratios (i.e., the ratio between observed and expected cases during follow-up) of outcomes among patients with RA. A sensitivity analysis with stratification of incidence rates by the number of prior bDMARD exposures will be conducted.

BSRBR-RA: Initial analyses will consist of comparisons in baseline status between the exposure cohorts. Analyses of endpoints will be based on comparing the risks of events over time using Cox-proportional hazards regression, taking into account differences between groups as potential confounders and effect modifiers. Control of confounding will be achieved by the use of propensity scores to balance the distribution of important confounders between exposure cohorts.

BIOBADASER: Descriptive analyses will include rates of events of interest within stratified treatment cohorts. Results will be presented as mean and standard deviation or as number and percentages as appropriate. Incidence rates will be calculated as the number of events/person-time with 95% confidence intervals (CIs). Comparative analyses using multivariable modelling to account for potential confounding will also be performed, if sufficient a sample size is reached.

RABBIT: Descriptive analyses will include baseline patient information and cumulative rates of events of special interest and SAEs for each exposure cohort. Comparative analyses will be performed using Cox regression and its generalisations with multivariable adjustment to control confounding. Additional analyses with propensity score weighting will also be performed to balance the distribution of important confounders between exposure cohorts. Cox models and propensity score models will be customised to each outcome. A sensitivity analysis with stratification of incidence rates by the number of prior bDMARD exposures will be conducted.

**Milestones:**

AbbVie will initiate the study upon endorsement of the study protocol by the EMA. Study progress will be reported every year starting from 2022 to 2029. An interim report of study results will be submitted to the EMA approximately 5 years following market availability (anticipated in 2025), and the final study report will be submitted to the EMA in March 2030.

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