4.0 Abstract

Title:

Long-term 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). Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib recommended use in RA has been changed. Upadacitinib 15 mg is approved to be used in the EU for treatment of elderly patients ≥ 65 years of age or patients with risk factors for malignancy, major adverse cardiovascular events (MACE) or venous thromboembolism (VTE). In addition, upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors.

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.

Research Question and Objectives:

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

1. To assess comparability across users of upadacitinib and other select systemic treatments for RA through in-depth assessments of drug utilisation and patient characteristics at baseline.
2. To describe the incidence of the following safety outcomes in patients with RA treated with upadacitinib:
    - Malignancy excluding non-melanoma skin cancer, including malignancy by type
    - Non-melanoma skin cancer (NMSC)
    - Major adverse cardiovascular events (MACE)
    - Venous thromboembolism (VTE)
    - Serious and opportunistic infections (including herpes zoster and tuberculosis)
    - Gastrointestinal perforations
    - Liver injury (including drug-induced liver injury)
    - Bone fractures
    - All-cause mortality
3. If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in patients with RA treated with upadacitinib relative to those treated other select systemic RA treatments (excluding other JAK inhibitors).

The secondary objectives are:

1. To describe the incidence of the safety outcomes mentioned under the primary objective among the following patient subcohorts of upadacitinib users: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), and patients with severe renal impairment (when possible using proxy measures available within a given data source).
2. If a suitable comparator is identified, to describe the incidence of the safety outcomes mentioned under primary objectives in the following patient subcohorts of other select systemic RA treatments: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), and patients with severe renal impairment (when possible using proxy measures available within a given data source).

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 for the treatment of RA and when feasible, compared to patients exposed to select (non-JAK inhibitor) standard of care systemic RA treatments. A new user, active comparator cohort study design will be used. 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.

Importantly, labelling changes following the Article 20 procedure are likely to result in substantial differences in baseline characteristics of patients initiating upadacitinib and those initiating other systemic treatments. Therefore, initial in-depth descriptive analyses will be conducted to assess comparability across treatment cohorts and inform the design (including selection of suitable comparator/s) of subsequent analyses.

Population:

The source population 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. Other select systemic treatments for RA (i.e., potential comparators) will include the following:

ARTIS and DANBIO (Sweden and Denmark):

- *bDMARD users:* Patients with RA initiating a bDMARD treatment (can be stratified into patients initiating their first, second, and third biologic)
- *Biologic naïve users:* 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 users:* 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 users:* 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 users*: Patients with RA initiating a bDMARD treatment

RABBIT (Germany):

- *bDMARD users:* Patients with RA initiating a bDMARD treatment (can be stratified into patients initiating their first, second, and third biologic)
- *Biologic naïve DMARD users:* 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 non-melanoma skin cancer [NMSC]), serious and opportunistic infections (including herpes zoster and TB), MACE, VTE, all-cause mortality, GI perforations, acute liver injury (including DILI), and bone fractures. 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 Swedish and Danish 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 potential 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. In each Denmark and Sweden, a cohort of at least 2,000 upadacitinib-exposed patients and at least 2,000 in each potential comparator cohort (bDMARD/anti-TNFα users and biologic naïve users) 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:

To inform comparability across treatment cohorts following the referral procedure, descriptive analyses will first be conducted to characterise users at baseline (e.g., demographics, co-morbidities, concomitant medications, RA treatment experience, RA disease activity, and healthcare utilisation) and the real-world utilisation of upadacitinib and other select systemic treatments for RA, overall for each registry, and by age group, relevant risk factors (e.g.; malignancy, MACE, VTE), calendar time of index date (pre/post SmPC updates), and disease history as listed in the secondary objectives. Appropriate statistics (e.g., Standardized Mean Difference [SMD]) will be used to assess

comparability across treatment groups. When possible according to registry-specific methods, the distribution/overlap of propensity scores across treatment groups may also be examined to assess the balance across cohorts. These descriptive analyses will also provide guidance on feasibility of comparing incidence rates across treatment cohorts.

Person-years at risk, the number of safety outcomes observed, and crude incidence rates for the upadacitinib cohort will be reported overall by each registry and across relevant stratifications and subgroups. If suitable/comparable treatment cohorts can be identified, crude incidence rates for all safety outcomes will also be provided for selected comparator cohorts treated with other select systemic RA treatments.

If assessed as feasible for a safety outcome of interest, based on (1) number of upadacitinib users, (2) number of other select systemic RA treatment users suitable for comparison, and (3) number of safety events observed, comparative analyses will be performed by the registry to compare upadacitinib and comparator treatments in the final report.

Relevant subgroup and sensitivity analyses will be conducted as well.

Registry-specific details for descriptive and comparative analyses (as deemed feasible) are described below.

ARTIS and DANBIO: Descriptive analyses will include baseline patient information and incidence rates of events of special interest for each identified 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 identified 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 the identified 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 incidence rates of events of special interest and SAEs for each identified 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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