4.0 Abstract

Title:

Long-term safety study of Rinvoq™ in RA patients enrolled in the CorEvitas RA Registry in the United States

Version 3.0, 12 September 2023

Rationale and Background:

Rinvoq is a potent, selective inhibitor of Janus kinase (JAK) with demonstrated efficacy in the treatment of moderately to severely active rheumatoid arthritis (RA). Safety has been characterized during the development program, however, additional evaluation of safety, particularly for rare events and events with long latency outcomes, in the broader RA population is warranted. To provide this evidence, AbbVie plans to implement a post-approval, population-based prospective cohort study in partnership with the CorEvitas United States (US) RA Registry. The study is designed to evaluate the important identified and potential risks outlined in the European Union (EU) Risk Management Plan (RMP) for Rinvoq (upadacitinib) and in patient groups for whom there is limited information (i.e., "missing information" in the EU-RMP). To that end, the study is sufficiently powered to identify clinically meaningful increases in the risk of adverse events including malignancies, venous thromboembolic events (VTE), major adverse cardiovascular events (MACE), and serious infection events (SIE) in patients treated with Rinvoq relative to patients treated with biologic medications approved for the treatment of moderately to severely active RA. In consideration of findings of the ORAL Surveillance study and changes to the RINVOQ Summary of Product Characteristics (SmPC) warnings and precautions text that occurred in 2023, assessment of the appropriate comparators will be conducted across various risk factors, in addition to the assessment of the impact of the additional risk minimization measures (aRMM) on study outcomes.

The CorEvitas (formerly Corrona) RA Registry was established in 2001 and includes data from over 54,074 RA patients, treated by 817 physicians, located at 189 sites, in 42 states. The currently active site network includes 82 sites, 279 physicians, and 25,052 patients, as of December 31, 2019. Detailed data collection by participating CorEvitas investigators and their patients with RA enables capture of major clinical and patient-reported outcomes, as well as detailed comorbidity and safety information. To support post authorization safety studies, CorEvitas has implemented additional questionnaires for reporting details of serious adverse events and adverse events of special interest on customized Targeted Adverse Event Questionnaires (TAEQ). TAEQs have been implemented for the primary outcomes of the proposed study (malignancy, MACE, SIE and VTE), with VTE TAEQ implemented in May 2019.

CorEvitas has experience conducting prior biomarker sub-studies, nested within the RA Registry, with sites collecting blood for central laboratory testing as well as biosamples for storage in a biorepository. A subset of the total Rinvoq Post-Authorization Safety Study (PASS) patient population initiating Rinvoq or a comparator biologic for the first time will be recruited and enrolled in a CorEvitas Rheumatology Biomarker Study whereby a panel of VTE risk-related laboratory tests will be performed centrally, and additional DNA, RNA, plasma and serum samples will be collected. Laboratory results and clinical data will be examined descriptively to characterize the association between biomarkers and VTE risk. Longer term biobanking of patient samples will also be employed to allow for potential future evaluation of to-be-discovered biomarkers related to VTE risk.

Research Question and Objectives:

The overall goal of the study is to characterize the safety of Rinvoq in RA patients in the post-approval setting.

Primary Objective:

- To compare the incidence of malignancy (excluding non-melanoma skin cancer; NMSC), NMSC, MACE, VTE, SIE, and mortality in adults with RA who receive Rinvoq relative to those who are treated with biologic medications approved for the treatment of RA, in the course of routine clinical care.

Secondary Objectives:

- To describe the incidence rates of the following adverse events: herpes zoster (HZ), opportunistic infections (OI), active tuberculosis (TB), gastrointestinal (GI) perforations, bone fractures, and evidence of drug-induced liver injury (DILI) in adults with RA who receive Rinvoq relative to those who are treated with biologic medications approved for the treatment of RA, in the course of routine clinical care.
- To describe the incidence of the above adverse events in elderly patients aged ≥ 75 years.
- To describe the incidence rates of malignancy (excluding NMSC), NMSC, MACE, VTE, SIE, HZ, OI, GI perforations, bone fractures, DILI, and mortality in the following subgroups of interest:
  - Patients with moderate hepatic impairment at the time of Rinvoq or biologic therapy start
  - Patients with evidence of chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) at the time of Rinvoq or biologic therapy start
  - Patients with severe renal impairment at the time of Rinvoq or biologic therapy start

Exploratory Objective:

- To describe the distribution of risk factors for VTE in those treated with Rinvoq and those treated with biologic therapy, and in those who do and do not experience VTE during follow-up, in a subset of participating patients providing laboratory samples.

Study Design:

Patients initiating Rinvoq or biologic medications for the treatment of RA will be recruited by registry sites to enroll in the CorEvitas RA Registry. Patients enrolled in the registry and eligible for the Rinvoq post-authorization safety study, henceforth Rinvoq PASS, will automatically be enrolled and contribute data for planned Rinvoq PASS analyses. The Rinvoq PASS is a prospective, observational cohort study that will be conducted within the broader CorEvitas RA Registry. Data from these patients will be used to produce a set of drug exposure cohorts that will be used to accomplish the analytic objectives of this Rinvoq PASS protocol.

The drug exposure cohorts will be a Rinvoq exposure cohort and a biologic exposure cohort.

Biosample collection and testing for markers of VTE risk will be employed in exploratory studies for a sub-set of the Rinvoq PASS patients, to enable conduct of the exploratory objective. In addition, samples will be banked for potential future analyses of biomarkers associated with VTE risks.

Population:

The population for the Rinvoq PASS will be drawn from patients enrolled in the CorEvitas US RA Registry. The CorEvitas US RA Registry is an established, prospective, multicenter, observational registry for adult patients with RA. Patients receiving Rinvoq or a comparator biologic will be eligible for inclusion in the CorEvitas RA Registry, and the planned Rinvoq PASS analyses, specifically.

Study eligibility criteria include all CorEvitas US RA registry inclusion criteria and additionally requires that a patient is treated with Rinvoq, or a biologic medication during the study period. A patient must not meet any registry exclusion criteria.

Variables:

Longitudinal data are obtained via CorEvitas US RA questionnaires. Questionnaires are completed by both patients and their treating rheumatology health care providers during routine clinical visits.

Patient Questionnaires capture subject demographics, lifestyle factors, medical history, family history, comorbid conditions, and the following patient-reported outcome measures:

- Patient Global Assessment
- Pain, and Fatigue Visual Analog Scales (VAS 0-100)
- Patient Global Assessment for RA patients (VAS 0-100)
- Functional status (HAQ-DI, EQ-5D-3L)

Provider Questionnaires capture RA disease duration, measures of RA disease activity and severity, RA treatment history and current biologic, conventional synthetic disease modifying anti-rheumatic drug (DMARD) and targeted synthetic DMARD use (including JAK inhibitors). Specifically, the following clinical assessments are captured:

- 28 Tender and Swollen Joint counts
- Investigator Global Assessment (VAS 0-100)
- Calculated CDAI (Clinical Disease Activity Index), SDAI (Simple Disease Activity Index), DAS28 (Disease Activity Score)
- Rheumatoid factor
- Anti-CCP antibody status
- Radiographic evidence of erosions
- Serious and non-serious Adverse Events

Targeted Adverse Event Questionnaires (TAEQs) are completed by the Provider to capture detailed risk factor, confirmatory testing, and other clinical characteristics for serious adverse events and registry-defined adverse events of special interest,

e.g., Malignancy, serious infection events (SIE), major adverse cardiovascular event (MACE), venous thromboembolic events (VTE).

Additional questionnaires capturing supplemental details include: Laboratory Assessments, Personal Identifying Information (for linkage to external data sources), and Subject Exit.

Additional laboratory samples will be collected from a subset of registry sites and participants through the CorEvitas Rheumatology Biomarker Study. Blood collection for the CorEvitas Rheumatology Biomarker Study is not mandatory. Eligible patients may participate in the CorEvitas RA Registry and the Rinvoq PASS, regardless of whether they also consent to blood collection through the CorEvitas Rheumatology Biomarker Study.

Potential biomarkers for increased risk of VTE and increased risk of VTE when treated with Rinvoq will be explored in a subset of patients participating in Rinvoq PASS who have also consented to sample collection. Samples will be collected before receiving the first dose of Rinvoq or biologic. Samples will be processed and shipped to a designated central laboratory for analysis. A portion of the sample will be banked for potential future analyses of biomarkers associated with VTE risks.

Data Sources:

The Rinvoq PASS will be conducted using data collected in the CorEvitas US RA Registry. Data are collected through detailed questionnaires and source documents submitted by participating providers and patients in the context of routine clinical care.

A subset of CorEvitas registry sites will collect plasma, serum, RNA and DNA.

Study Size:

Sample sizes of 2,500 and 5,000 patients are planned for the Rinvoq and biologic cohorts, respectively. Accrual for this study is estimated to take 5 years, and follow-up will

continue for a minimum of 5 years from the inclusion of the last patient, for a total study duration of 10 years. The study was designed to achieve at least 90% power to detect an increased risk of malignancy with Rinvoq (hazard ratio [HR] of 1.5 or greater) and to achieve 80% power to detect an increased risk of VTE with Rinvoq (HR of 2.0 or greater) and other secondary endpoints. The malignancy calculations assumed a 0.86 incidence rate of malignancy excluding NMSC in the biologic exposure cohort. The non-malignancy calculation assumed a 0.61 incidence rate of VTE in the biologic exposure cohort and an average of 1.5 years exposed to treatment in both cohorts.

Data Analysis:

The population of patients in the study will be characterized with respect to demographic, clinical, disease and patient-reported outcomes using descriptive statistics. The main analyses will employ propensity score methods to address confounding by indication (channeling bias) followed by estimation of incident rates as well as multivariable Cox proportional hazards modeling to estimate HRs and associated 95% CIs. The analysis of the primary malignancy and non-malignancy outcomes will occur at the completion of the 5-year follow-up period (following last accrued patient). An interim analysis of VTE, MACE, SIE, and mortality will also be conducted and is planned to occur when enough events have been observed in the Rinvoq and comparator cohorts combined (~74 VTE events) to achieve 80% power to detect a HR of 2.0. The number of events will be monitored annually, and an analysis will commence when the required number of events has occurred.

Analyses of the secondary outcomes will be descriptive and include estimating the incidence rate of HZ, OI, GI perforations, bone fractures, and DILI. Several subgroups of patients with risk factors of interest (e.g., history of renal insufficiency, hepatitis B or C, DILI, hepatotoxicity) will also be examined with respect to the primary and secondary outcomes.

Available laboratory markers will be described in the Rinvoq PASS population overall and qualitatively compared between patients who do and do not experience a VTE while exposed to Rinvoq or biologic therapy.

Milestones:

- Start of data collection: 16 August 2019
- End of data collection: Approximately 10 years post-approval
- Interim report: Approximately 8 years post-approval
- Final study report: Approximately 10.5 years post-approval

Investigators:

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5.0 Amendments and Updates

The protocol version 3, dated 13 September 2023, is the amended protocol addressing administrative changes and comments from the PRAC Rapporteur.