Swiss Summary of the Risk Management Plan (RMP)

14 Juni 2024

RINVOQ®

(Upadacitinib)

15 mg, 30 mg, and 45 mg

Prolonged-release tablets

Based on EU RMP, Version 13.5 (August 2023)

AbbVie AG

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of RINVOQ® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of RINVOQ® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AbbVie AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of RINVOQ®.

Summary of risk management plan for Rinvoq™ (upadacitinib)

This is a summary of the risk management plan (RMP) for Rinvoq. The RMP details important risks of Rinvoq, how these risks can be minimized, and how more information will be obtained about Rinvoq's risks and uncertainties (missing information).

Rinvoq's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Rinvoq should be used.

This summary of the RMP for Rinvoq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rinvoq's RMP.

I The Medicine and What it Is Used For

Rinvoq is authorized for the treatment of:

- Rheumatoid arthritis (RA)
- Psoriatic arthritis (PsA)
- Ankylosing spondylitis (AS)
- Non-radiographic axial spondyloarthritis (nr-axSpA)
- Atopic dermatitis (AD)
- Ulcerative colitis (UC)
- Crohn's disease (CD)

See the SmPC for full indication statements. Rinvoq contains upadacitinib as the active substance and it is given orally.

Further information about the evaluation of Rinvoq's benefits can be found in Rinvoq's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

II Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Rinvoq, together with measures to minimize such risks and the proposed studies for learning more about Rinvoq's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Rinvoq, these measures are supplemented with additional risk minimization measures (aRMMs) mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Rinvoq is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Rinvoq are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rinvoq. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Serious and opportunistic infections including tuberculosis (TB) • Herpes zoster • Non-melanoma skin cancer (NMSC) • Gastrointestinal (GI) perforation
Important potential risks	• Malignancies excluding NMSC • Major adverse cardiovascular event (MACE) • Venous thromboembolic events (VTEs) (deep venous thrombosis and pulmonary embolus) • Drug-induced liver injury (DILI) • Fetal malformation following exposure in utero • Fractures
Missing information	• Use in very elderly (≥ 75 years of age) • Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C • Use in patients with moderate hepatic impairment • Use in patients with severe renal impairment • Long-term safety • Long-term safety in adolescents with AD

II.B Summary of Important Risks

Important identified risk 1: Serious and opportunistic infections including TB	
Evidence for linking the risk to the medicine	Approved therapies of the Janus kinase (JAK) inhibitor class are associated with or are being investigated for risk of serious infections and opportunistic infections. Serious and opportunistic infections including TB were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Advanced age and background immunosuppressive medications such as concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and prednisone are common in the moderate to severe active RA and PsA populations and can also be found in the AS and nr-axSpA populations, although to a lesser extent, and systemic corticosteroids such as prednisone are common in the moderate to severe active AD, UC, and CD populations, placing these populations at increased risk. Corticosteroids and csDMARDs are not recommended for axial symptoms in AS and nr-axSpA; therefore, immunosuppressive medication burden is smaller than in RA or PsA. Eczema herpeticum (EH) is an infection that has been associated with AD and is the most commonly recognized viral complication in patients with AD (Beck 2009).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose-dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on absolute lymphocyte count and absolute neutrophil count. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with chronic or recurrent infections.

	• A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of direct healthcare professional communication (DHPC) in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the United States (US) • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Study P20-390: Long-Term safety study of upadacitinib use in AD patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (biologic disease-modifying anti-rheumatic drug inadequate responder [bDMARD-IR] AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk 2: Herpes zoster	
Evidence for linking the risk to the medicine	Approved therapies of the JAK inhibitor class show increased risk of herpes zoster in patients with RA, PsA, AS, nr-axSpA, AD, UC, and CD. Herpes zoster was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and in AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Herpes zoster is caused by reactivation of latent varicella zoster virus; therefore, it can only occur in patients who have previously been infected with varicella zoster virus. Herpes zoster occurs most frequently among older adults and immunocompromised persons such as patients using immunomodulatory products or immunosuppressive products. Advanced age and background immunosuppressive medications such as concomitant csDMARDs and prednisone are common in the moderate to severe active RA and PsA populations, and can also be found in the AS and nr-axSpA populations, and systemic corticosteroids such as prednisone are common in the moderate to severe active AD, UC, and CD populations, placing these populations at increased risk. As anticipated based on published literature regarding herpes zoster in these conditions, prior herpes zoster and advanced age were risk factors for the development of herpes zoster while receiving upadacitinib. Additionally, a higher rate of herpes zoster was seen in the Asian region, as reported with other JAK inhibitors (Winthrop 2014).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current immunization guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational guide • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US

	• Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Study P20-390: Long-Term safety study of upadacitinib use in AD patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk 3: NMSC	
Evidence for linking the risk to the medicine	NMSC was assessed in data from upadacitinib clinical trials described below and from the company post-marketing database. An analysis of NMSC was performed to evaluate NMSC using the pooled data from all unblinded and open label extension upadacitinib studies as of 15 August 2021. The data analysis showed that the crude overall rate of NMSC was higher with upadacitinib 30 mg (0.62 events per 100 PY) compared with upadacitinib 15 mg (0.38 events per 100 PY), with a hazard ratio of 1.76 (95% CI, 1.20 to 2.58; stratified by indication, p = 0.004). The higher incidence of NMSC with upadacitinib 30 mg emerged after approximately 1 year of upadacitinib treatment as compared to the 15 mg dose and continued to increase beyond 1 year. Additionally, the proportion of subjects with recurrent NMSC was higher with upadacitinib 30 mg as compared to upadacitinib 15 mg. These observations further suggest a potential higher risk of NMSC over long-term exposure with upadacitinib 30 mg compared with upadacitinib 15 mg.
Risk factors and risk groups	Inflammation is considered a key process in skin tumorigenesis (Neagu 2019). Patients with inflammatory diseases such as RA and inflammatory bowel disease (IBD) have higher risks of NMSC than the general population (Raaschou 2016, Singh 2011). Immunosuppressive medications, such as methotrexate (MTX) and tumor necrosis factor (TNF) inhibitors, have been found to be associated with a higher risk of NMSC (Assassi 2016). Basal cell carcinoma (BCC) (a type of NMSC) develops primarily on sun-exposed skin; thus, ultraviolet (UV) radiation plays a critical role in the pathogenesis of BCC. The occurrence of BCC increases as the population ages and approximately 80% of all BCC's are diagnosed above age 55 years (Ciążyńska 2021). The most critical

	risk factor for squamous cell carcinoma (a type of NMSC) is UV radiation from sunlight exposure (Fagan 2023). Traditional risk factors of NMSC such as cumulative UV exposure, radiation therapy, prolonged immunosuppression, human papillomavirus infection, smoking, lower Fitzpatrick skin types, and other genetic risk factors also apply in patients with RA, PsA, AS, nr-axSpA, AD, UC, and CD.
Risk minimization measures	Routine risk minimization measures: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. <u>Additional risk minimization measures:</u> • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the United States (US) • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of RA • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

	• Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk 4: GI perforation	
Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for risk of GI perforation. GI perforation was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Risk factors for GI perforations include history of diverticulitis, use of glucocorticoids, exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), increasing age, and higher levels of co-morbidity (Curtis 2012). Advanced age is common for RA and PsA patients, background immunosuppressive medications and NSAIDs are common in the moderate to severe active RA, PsA, AS, and nr-axSpA populations, and background immunosuppressive medications are common in the moderate to severe AD, UC, and CD populations placing these populations at increased risk. Use of tocilizumab, an interleukin-6 inhibitor, has been associated with increased risk for GI perforation (Monemi 2016, Strangfeld 2017). Patients with moderate to severe inflammatory bowel diseases (UC and CD) have an increased risk of GI perforation compared to the general population (McAuliffe 2015). In CD, patients with moderate to severe disease have a higher risk of intestinal/gastric perforations compared to those with mild disease (McAuliffe 2015).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Additional risk minimization measures: • HCP educational guide • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe

	• Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk 1: Malignancies excluding NMSC	
Evidence for linking the risk to the medicine	Malignancies were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	There is evidence that RA PsA, AD, UC, and CD patients have a higher occurrence of certain malignancies compared to the general population. The etiology of this finding may include immune dysregulation and/or chronic immune activation as seen in RA patients (Shah 2015) AD patients (Wang 2019), and UC and CD patients (Ullman 2011). Lymphoproliferative disorders occur with increased frequency in patients with RA and PsA (Smitten 2008), and patients with UC or CD exposed to specific therapies are at increased risk of lymphoproliferative disease (Beaugerie 2009, Kandiel 2005). The lymphoma incidence increases as active RA and PsA persists and correlates with the severity of disease activity (Baecklund 2006, Naschitz 2008). In addition to lymphoma, RA patients are at increased risk for lung cancer, and patients with CD are at increased risk of colorectal cancer (Olen 2020). Patients with AS and nr-axSpA have not been reported to have an increased risk of malignancy, with the exception of those exposed to spinal radiation treatment, with is no longer used (Exarchou 2016).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide

	• Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of RA • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 2: MACE	
Evidence for linking the risk to the medicine	Adjudicated MACE was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Traditional cardiovascular (CV) risk factors such as prior CV events, smoking, dyslipidaemia, obesity, hypertension, diabetes mellitus, and age also apply to patients with RA, PsA, AS, nr-axSpA, AD, UC, and CD. The potential for MACE in these patients as a result of elevations of lipid levels while on a JAK inhibitor or other therapies for these conditions remains unclear.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib.

	• SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk 3: VTEs (deep venous thrombosis and pulmonary embolus)	
Evidence for linking the risk to the medicine	Baricitinib, an approved JAK inhibitor with similar selectivity for JAK1 and JAK2, is being investigated for potential risk of thromboembolic events. It is not yet known if there is a role of JAK inhibition in the potential for developing VTEs. Adjudicated VTEs (deep venous thrombosis and pulmonary embolus) were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Risks for VTEs in the general population also apply to patients with RA, PsA, AS, nr-axSpA, AD, UC, and CD and include prior history of VTE, contraceptive use, obesity, malignancies, smoking, and inactivity such as bedrest following major surgeries like joint replacement. The general risk for VTE is increased in patients with AS especially in the first years after diagnosis (Aviña-Zubieta 2019). Patients with inflammatory bowel disease have an increased risk of VTE (Papa 2020), especially during periods of disease flare (Grainge 2010).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

	• Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 4: DILI	
Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for DILI. DILI was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Transaminase elevations can occur in the setting of RA, PsA, AS, and nr-axSpA independent of treatment (Robinson 1983, Takahashi 2010), and are commonly observed with NSAID and immunosuppressive treatment for these conditions, and with immunosuppressive treatment for AD, UC, and CD (Nygaard 2014, Restellini 2017, Takahashi 2010). Elevations have also been noted in AS patients treated with TNF inhibitors (Ghabril 2013).

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on transaminases. • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in alanine transaminase or aspartate transaminase are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 5: Fetal malformation following exposure in utero	
Evidence for linking the risk to the medicine	Approved therapies of the JAK inhibitor class are being investigated for potential risk of fetal malformation following exposure in utero. Nonclinical studies showed that upadacitinib is teratogenic in both rats and rabbits.
Risk factors and risk groups	Risk of fetal malformation pertains only to female patients of childbearing potential who become pregnant while receiving upadacitinib or and for at least 4 weeks after treatment.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy,

	and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female pediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Additional risk minimization measures: • HCP educational guide • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk 6: Fractures	
Evidence for linking the risk to the medicine	Results of a post hoc analyses of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors showed numerically higher risk for fractures with tofacitinib versus (vs.) TNF inhibitors (Hansen 2022). Events of fracture were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS and nr-axSpA clinical trial data.
Risk factors and risk groups	Risk factors for fractures include increasing age, female sex, previous fractures, underlying medical conditions, and use of medications such as glucocorticoids. Advanced age is common for RA and PsA patients, patients with RA are predisposed to osteoporotic fracture (Xue 2017), patients with AS are at increased risk of vertebral fracture (Vosse 2009), patients with CD and UC have a significant risk of fractures due to osteoporosis (Bernstein 2000), background use of corticosteroids is common in RA, PsA, UC, and CD, and both systemic and topical use is common in child and adult patients with AD (Ha 2022), placing these populations at increased risk.
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-824: A Study of Growth in Adolescents With AD Who Receive Upadacitinib • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information 1: Use in very elderly (≥ 75 years of age)

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomized study of tofacitinib (another JAK inhibitor). • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 2: Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if hepatitis B DNA is detected. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 3: Use in patients with moderate hepatic impairment	
Risk minimization measures	Routine risk minimization measures:

	• SmPC Section 4.2 describes use in patients with hepatic impairment. • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 4: Use in patients with severe renal impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with renal impairment. • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, and AD, the recommended dose is 15 mg once daily (QD) for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information 5: Long-term safety	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trials (Studies M14-465 and M15-555) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 6: Long-term safety in adolescents with AD	
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P20-390: Long-term safety study of upadacitinib use in AD patients • Study P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Rinvoq.

II.C.2 Other Studies in Post-Authorization Development Plan

Additional pharmacovigilance pharmacoepidemiology studies: Study P19-150: Long-term comparative safety cohort studies of upadacitinib use for the treatment of rheumatoid arthritis in Europe

Purpose of the studies: Although the upadacitinib clinical trials provide valuable information on the product's efficacy and safety, assessment of safety using randomized controlled trial (RCT) data is limited by the relatively small sample sizes and short duration of follow-up. Long-term safety data are needed in patients in routine clinical practice who are exposed to upadacitinib, including patients not included in the clinical program or in populations with limited clinical trial data (e.g., the very elderly, patients with evidence of untreated chronic infection with hepatitis B or hepatitis C, patients with moderate hepatic impairment, and patients with severe renal impairment). Several disease-based prospective rheumatology registries have been established in Europe to complement clinical trial data, including providing longitudinal safety data for new therapies.

Several of these European RA registries provide nearly complete national coverage of patients in a comprehensive electronic health record with multiple registry linkages and with low attrition over time. These registries allow for the evaluation of outcomes referent to an active user comparator group, and their large size provides the ability to study rare events not well captured in RCTs. As such, these registries have been used extensively to address post-marketing safety requirements in patients with RA, including comparative analyses of rates of infections, malignancy, adverse hepatic and renal events, and major adverse cardiovascular event (MACE). There is also demonstrated feasibility to evaluate venous thromboembolic event (VTE) risk in treated RA patient populations in these European RA registries (Davies 2011, Holmqvist 2012).

The aim of the study is to estimate the risks of serious and opportunistic infections (including active tuberculosis [TB] and herpes zoster), malignancy (excluding non-melanoma skin cancer [NMSC]), NMSC, MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular [CV] death), VTEs, gastrointestinal (GI) perforation, drug-induced liver injury (DILI) (hepatic injury), all-cause mortality, and fractures among individuals exposed to upadacitinib for the treatment of moderate to severe active RA, relative to similar patients receiving other approved therapies for the treatment of RA. When possible, the occurrence of the safety outcomes will be described in the very elderly, those with moderate hepatic impairment, those with severe renal impairment, and those with evidence of chronic infection with hepatitis B or hepatitis C.

Additional pharmacovigilance pharmacoepidemiology study: Study P19-141: Long-term safety study of upadacitinib in patients with rheumatoid arthritis enrolled in the Corrona RA Registry in the United States

Purpose of the study: Upadacitinib is a selective and reversible inhibitor of Janus kinase (JAK) with demonstrated efficacy in treatment of moderate to severe active RA. Safety has been characterized during the development program; however, additional evaluation of safety for rare events, long latency outcomes, and 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 Consortium of Rheumatology Researchers of North America (Corrona) United States (US) RA Registry. The study will be designed and sufficiently powered to identify clinically meaningful increases in the risk of malignancies, VTE, MACE, and serious infections in upadacitinib patients relative to patients treated with other therapies for moderately to severely active RA. A sub-study to explore thrombosis biomarkers at baseline in upadacitinib treated and comparator biologic treated patients will be conducted. In addition, biobanking will be employed to allow for

future evaluation of potential biomarkers related to VTE risk, should an increased risk be identified in upadacitinib treated patients.

The Corrona US RA Registry is an established, prospective, multicenter, observational registry for adult patients with RA. Established in 2001, Corrona includes data from over 52,500 RA patients, 750 physicians, and 182 sites, across 42 states. Detailed data collection by participating investigators and their patients with RA enables capture of a number of clinical, behavioral, and disease severity measures as well as clinical outcomes associated with treatment for RA. Data on targeted outcomes are collected prospectively, via Targeted Adverse Event Questionnaires. The overall goal of the study is to characterize the safety of upadacitinib in RA patients in the post-approval setting. The primary objective of the study is to compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA. A secondary objective is to describe the incidence rates of herpes zoster, opportunistic infections such as TB, GI perforations, evidence of DILI, all-cause mortality, and fractures. An additional secondary objective is to describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years). An exploratory objective is to characterize VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies.

Additional pharmacovigilance pharmacoepidemiology study: Study P20-199: Drug utilisation study of upadacitinib in Europe to evaluate the effectiveness of additional risk minimisation measures

Purpose of the study: As with other JAK inhibitors already marketed in Europe (e.g., tofacitinib and baricitinib), important safety risks have been identified with upadacitinib that require aRMMs. Using data derived from European RA registries, AbbVie plans to implement a drug utilization study to characterise the use of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card).

This study aims to evaluate the use of upadacitinib in routine clinical care through the following specific objectives:

1. To describe the baseline characteristics of new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use), and in a similar manner, to describe new users of a biologic disease-modifying anti-rheumatic drug (bDMARD) for comparison.
2. To evaluate the effectiveness of the aRMMs, including:
    - Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB;
    - Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib; and
    - Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring.

Additional pharmacovigilance pharmacoepidemiology study: Study P20-390: Cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden

Purpose of the study: Upadacitinib 15 mg was approved for the treatment of adults with moderate to severely active RA in the European Union on 18 December 2019. Studies to assess long-term safety of upadacitinib in the routine clinical setting for RA are currently being conducted.

Upadacitinib 15 mg is approved to be used in the EU for treatment of adolescents with moderate to severe AD weighing at least 30 kg. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib recommended use and doses have 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, MACE, or 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. An additional long-term safety study is proposed in order to assess the long-term safety of upadacitinib use in patients with moderate to severe AD in a real-world setting. The proposed study will be designed to evaluate and characterize the important identified and potential risks and missing information as described in this RMP.

The overall goal of the study is to characterize the safety of upadacitinib in AD patients in the post-approval setting. The primary objectives of the study are to assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline and to describe the incidence of the following outcomes, in adolescent and adult patients treated with upadacitinib, and compare (when feasible) the incidence of the above AEs relative to those treated with other alternative systemic drug therapies for AD, in the course of routine clinical care: Malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections (including opportunistic infections), herpes zoster, eczema herpeticum (EH)/Kaposi's varicelliform eruption, active TB, GI perforations, evidence of DILI, all-cause mortality, and fractures.

Secondary objectives are to describe the incidence of the above AEs in patients who receive upadacitinib by: dose of upadacitinib (15 mg and 30 mg); age groups (adolescents [12 – 17 years], adults aged 18 – 64 years, 65 – 74 years, and ≥ 75 years); history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) at the time of upadacitinib initiation; and history of severe renal impairment at the time of upadacitinib initiation, and, if a suitable comparator is identified, to describe the incidence of the above AEs in patients who receive other select systemic AD treatments.

Additional pharmacovigilance pharmacoepidemiology study: Study P21-825: Effectiveness evaluation of additional risk minimisation measures for upadacitinib in the treatment of atopic dermatitis

Purpose of the study: Additional risk minimization is being used for upadacitinib in RA and is proposed for upadacitinib in AD. Specific risks included in upadacitinib's risk minimization program will require aRMMs. AbbVie plans to evaluate the effectiveness of the aRMMs (HCP educational guide and patient card).

This study aims to evaluate the effectiveness of the aRMMs for upadacitinib in AD with the following specific objectives:

- Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB;
- Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib;
- Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring;

- Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.

Additional pharmacovigilance pharmacoepidemiology activity: Effectiveness evaluation of additional risk minimisation measures for upadacitinib in the treatment of rheumatoid arthritis

Feasibility of adding the following objectives to an existing upadacitinib study will be evaluated

Purpose of the study: Additional risk minimization is proposed for upadacitinib in RA. Specific risks included in upadacitinib's risk minimization program will require aRMMs. AbbVie plans to evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in a drug utilization study.

This study aims to evaluate the effectiveness of the aRMMs for upadacitinib in RA with the following specific objectives:

- Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.

Additional pharmacovigilance pharmacoepidemiology study: Study P21-824: A study of growth, development and maturation in adolescents with atopic dermatitis who receive upadacitinib

Purpose of the study: Upadacitinib 15 mg and 30 mg once daily (QD) are approved for use in adults with moderate to severe AD and upadacitinib 15 mg QD is approved for use in adolescents with moderate to severe AD weighing 30 kg or over and elderly patients ≥ 65 years of age. The available nonclinical data for upadacitinib do not suggest a risk associated with bone development in patients ≥ 12 years old. However, since the long-term use of upadacitinib on growth in adolescents has not been studied, the impact of long-term use of upadacitinib on growth in adolescents is not known.

Per Pharmacovigilance Risk Assessment Committee's (PRAC's) request, this study aims to evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAKi systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated. The primary objective is to compare differences in changes from baseline in height standard deviation score (SDS) and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.

The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, body mass index (BMI), BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.

Additional pharmacovigilance pharmacoepidemiology study: Cohort study of long-term safety of upadacitinib for the treatment of ulcerative colitis and Crohn's disease in a real-world setting in Europe

Purpose of the study: The primary objectives of the study are to describe and compare the incidence of the safety outcome GI perforation, and to describe and compare, where possible, the incidence of fractures and DILI, in adult individuals with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy.

The secondary objectives are to describe and, where possible, to compare the incidence of the following safety outcomes in adult individuals with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality.

In addition, incidence of the above clinical events will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program:

- Very elderly (aged ≥ 75 years);
- Patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies;
- Patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies;
- Patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies.

Additional pharmacovigilance pharmacoepidemiology study: Study P23-479: Drug utilisation study for evaluation of the effectiveness of additional risk minimisation measures for upadacitinib in the treatment of ulcerative colitis in Sweden and Denmark

Purpose of the study: Additional risk minimization is being used for upadacitinib in RA and is proposed for upadacitinib in UC. Specific risks included in upadacitinib's risk minimization program will require aRMMs. AbbVie plans to describe the baseline characteristics of new users of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in a drug utilisation study.

This study aims to evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives:

1. To describe the baseline characteristics of UC patients who are new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use), and in a similar manner, to describe new users of biologic therapies for comparison;
2. To describe the prescribing patterns of upadacitinib 45 mg for induction and 15 mg and/or 30 mg for maintenance in patients with UC, specifically:
    - To quantify the number of patients and describe baseline characteristics of patients with UC who receive upadacitinib induction dose (45 mg) for 8 weeks and greater than 8 weeks

- To quantify the number of patients and describe baseline characteristics of patients with UC who receive upadacitinib by maintenance dosing pattern (15 mg and 30 mg)

3. Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB;
4. Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib;
5. Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring;
6. Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.

Long-term extension portion of upadacitinib clinical trials

Study M14-465:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

Study M15-555:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

Study M15-554:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Study M15-572:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Study M19-944 (Study 1):

Purpose of the study: To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active biologic disease-modifying anti-rheumatic drug inadequate responder (bDMARD-IR) AS (Study 1), who have completed the Double-Blind Period.

Study M19-944 (Study 2):

Purpose of the study: To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.

Study M16-045:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with AD who have completed the Double-Blind Period.

Study M16-047:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg and 30 mg QD in combination with topical corticosteroids in subjects with AD who have completed the Double-Blind Period.

Study M18-891:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with AD who have completed the Double-Blind Period.

Study M14-533:

Purpose of the study: To evaluate the long-term safety and efficacy of upadacitinib in subjects with UC.

Study M14-430 Substudy 2:

Purpose of the study: To evaluate the safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.