Swiss Summary of the Risk Management Plan (RMP)

RINVOQ®

(Upadacitinib)

15 mg

Prolonged-release tablets

Version 2 (26 November 2021)

Based on EU RMP, version 2.3, 3.3 and 4.0

AbbVie AG, Cham

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®.

Part VI: Summary of the Risk Management Plan

I The Medicine and What it Is Used For

Rinvoq is authorized for the treatment of:

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Atopic dermatitis

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 EMA 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 analysed 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 TB • Herpes zoster
Important potential risks	• Malignancies • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • GI perforation • DILI • Foetal malformation following exposure in utero
Missing information	• Use in very elderly (≥ 75 years of age) • Effect on vaccination efficacy • 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

DILI = drug-induced liver injury; GI = gastrointestinal; MACE = major adverse cardiovascular event; TB = tuberculosis; VTEs = venous thromboembolic events

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 clinical trial data, and AS 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 moderately to severely active RA and PsA populations, and can also be found in the AS population, although to a lesser extent, and systemic corticosteroids such as prednisone are used in the moderate to severe active AD population, placing these populations at increased risk. Eczema herpeticum 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.

	• 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 will describe 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 active, 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 immuno-compromised 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. Additional risk minimization measures: • HCP educational brochure • Patient Alert Card (PAC)
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe

	• Long-Term Safety Study of Upadacitinib Use in RA Patients in the United States (US) • Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Effectiveness Evaluation of Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) 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, and AD. Herpes zoster was assessed in integrated upadacitinib RA, integrated PsA, integrated AD clinical trial data, and AS 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 immuno-suppressive 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 population, and systemic corticosteroids such as prednisone are used in the moderate to severe active AD population, placing these populations at increased risk. As anticipated based on published literature regarding herpes zoster in patients with RA, PsA, AS and AD, 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 if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational brochure • PAC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Effectiveness Evaluation of Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk 1: Malignancies	
Evidence for linking the risk to the medicine	Approved therapies of the JAK inhibitor class are being investigated for potential risk of malignancies.

	Malignancies were assessed in integrated RA, integrated PsA, integrated AD clinical trial data, and AS clinical trial data.
Risk factors and risk groups	There is evidence that RA, PsA, and AD 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) and AD patients (Wang 2019). Lymphoproliferative disorders occur with increased frequency in patients with RA and PsA (Smitten 2008). 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. Patients with AS 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). Traditional risk factors of non-melanoma skin cancer such as cumulative ultraviolet 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, and AD.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the risk in patients with RA and indicates that upadacitinib clinical data are currently limited and long-term studies are ongoing. • The PL warns that patients who have cancer, develop a new lesion or any change in the appearance of an area on the skin, or are at high risk of developing skin cancer should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises that periodic skin examination is recommended for patients who are at increased risk for skin cancer. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis

	• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) 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	Approved JAK inhibitors are being investigated for potential risk of MACE. Adjudicated MACE was assessed in integrated upadacitinib RA, integrated PsA, integrated AD clinical trial data, and AS 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, and AD. 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 contains a section on CV risk including a statement on increased CV risk in RA patients and need for management of CV risk factors as part of usual standard care. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • The PL warns that patients who have heart problems, high blood pressure, or high cholesterol should consult their doctor or pharmacist before and during treatment with Rinvoq. Additional risk minimization measures: • HCP educational brochure • PAC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US

	• Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Effectiveness Evaluation of Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) 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 equal 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 clinical trial data, and AS clinical trial data.
Risk factors and risk groups	Risks for VTEs in the general population also apply to patients with RA, PsA, AS, and AD and include prior history of VTE, contraceptive use, obesity, malignancies, smoking, and inactivity such as bedrest following major surgeries like joint replacement.
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 patients receiving JAK inhibitors including upadacitinib. • The PL warns that patients who have had blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism) should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath. • SmPC Section 4.4 advises that upadacitinib should be used with caution in patients at high risk for deep vein thrombosis/pulmonary embolism. Risk factors that should be considered in determining the patient's risk

	for deep venous thrombosis/pulmonary embolism include older age, obesity, a medical history of deep venous thrombosis/pulmonary embolism, patients undergoing major surgery, and prolonged immobilisation. • SmPC Section 4.4 advises that if clinical features of deep vein thrombosis/pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. Additional risk minimization measures: • HCP educational brochure • PAC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Effectiveness Evaluation of Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 4: GI perforation	
Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for potential risk of GI perforation. GI perforation was assessed in integrated upadacitinib RA, integrated PsA, integrated AD clinical trial data, and AS 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 and background immunosuppressive

	medications and NSAIDS are common in the moderately to severely active RA population, PsA, and AS populations, and background immunosuppressive medications are common in the moderate to severe AD 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).
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 5: 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 clinical trial data, and AS clinical trial data.
Risk factors and risk groups	Transaminase elevations can occur in the setting of RA, PsA, AS, and AD, independent of treatment (Takahashi 2010, Robinson 1983) and are commonly observed with NSAID and immunosuppressive treatment in these conditions. A large cohort study of RA subjects enrolled in the Consortium of Rheumatology Researchers of North America (Corrona) identified elevated alanine transaminase (ALT)/aspartate transaminase (AST) levels in 14% – 31% of RA patients treated with csDMARDS, including methotrexate (MTX) (22%) (Curtis 2010). The same cohort identified 6% of subjects treated with tumor necrosis factor (TNF) inhibitors who experienced ALT/AST

	increases (Sokolove 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 ALT or AST 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: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 6: Foetal 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 foetal malformation following exposure in utero. Nonclinical studies showed that upadacitinib is teratogenic in both rats and rabbits.
Risk factors and risk groups	Risk of foetal 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. Additional risk minimization measures: • HCP educational brochure • PAC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • Effectiveness Evaluation of Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) 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 aged 75 years and older. • SmPC Section 4.8 states that there was a higher rate of serious infections in patients ≥ 75 years of age, although data are limited. • SmPC Section 4.4 states that as there is a higher incidence of infections in the elderly ≥ 75 years of age, caution should be used when treating this population. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

	• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 2: Effect on vaccination efficacy	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 includes language that no data are available on the response to vaccination with live or inactivated vaccines in patients receiving upadacitinib. • SmPC Section 4.4 states that use with live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended. • SmPC Section 4.4 includes language that prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunisations in agreement with current immunisation guidelines. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Vaccination substudy See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 3: 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: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 4: 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: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 5: 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. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 6: 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	Additional pharmacovigilance activities:

activities	• Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Long-term Cohort Study of Upadacitinib Safety in the Treatment of Atopic Dermatitis • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 2/3 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) See Section II.C of this summary for an overview of the post-authorization development plan.

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

Vaccination substudy
Purpose of the study: Immune response to vaccination has not been studied in subjects who receive a vaccination while on upadacitinib therapy. Immunomodulatory medications used to treat RA, PsA and AD, including JAK inhibitors, have the potential to impair immune responses to vaccinations. The objective of this substudy was to assess the impact of upadacitinib treatment (15 mg once daily [QD] or 30 mg QD) with a stable background of MTX on immunological responses following administration of Prevnar 13® pneumococcal vaccine in RA patients. The study has been completed and data are under review.

Additional pharmacovigilance pharmacoepidemiology studies: long-term comparative safety cohort studies of upadacitinib use for the treatment of RA 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 MACE. There is also demonstrated feasibility to evaluate 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 TB and herpes zoster), malignancies, MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or CV death), VTEs, GI perforation, and DILI (hepatic injury) 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: long-term comparative safety cohort study of upadacitinib use for the treatment of RA in the US
Purpose of the study: Upadacitinib is a selective and reversible inhibitor of JAK with demonstrated efficacy in treatment of moderate to severely 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 Corrona 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, behavioural, 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 non-melanoma skin cancer [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, and evidence of DILI. 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: drug utilisation study of upadacitinib in Europe to evaluate the effectiveness of aRMMs

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 utilisation study to characterise the use of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational brochure and PAC).

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 DMARD (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: long-term cohort study of upadacitinib safety in the treatment of AD

Purpose of the study: Upadacitinib 15 mg was approved for the treatment of adults with moderate to severely active RA in the EU 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 proposed to be used in the treatment of adolescents with moderate to severe AD weighing at least 40 kg and upadacitinib 15 mg or 30 mg for treatment of adults with moderate to severe AD. 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 the important identified and potential risks as described in the accompanying RMP. Additionally, rates of these events will be described to better understand safety in populations with limited or missing information from the clinical development program.

The overall goal of the study is to characterize the safety of upadacitinib in AD patients in the post-approval setting. The primary objective of the study is to compare the incidence of the following outcomes, in adolescent and adult patients treated with upadacitinib 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, herpes zoster, opportunistic infections, eczema herpeticum/Kaposi's varicelliform eruption, active TB, GI perforations, and evidence of DILI. A secondary objective is to describe the incidence of the above adverse events in elderly patients aged ≥ 75 years. An exploratory objective is

to describe the incidence rates of the above safety outcomes in the following subgroups of interest, with limited or missing information from the clinical development program.

- Patients with moderate hepatic 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
- Patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies

Additional pharmacovigilance pharmacoepidemiology study: Effectiveness evaluation of additional risk minimisation measures for upadacitinib in the treatment of AD in Europe

Purpose of the study: Upadacitinib 15 mg and 30 mg is proposed to be used in adults with AD and upadacitinib 15 mg is proposed to be used in adolescents with AD weighing at least 40 kg. Additional risk minimization (aRMz) is being used and is proposed for upadacitinib in AD. Specific risks included in upadacitinib's aRMz program will require aRMMs. AbbVie plans to evaluate the effectiveness of the aRMMs (HCP educational brochure and PAC).

This study aims to evaluate the effectiveness of the aRMMs 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; and
- Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring.

Long-term extension portion of Phase 3 upadacitinib trials

Study M13-542:
Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.

Study M13-549:
Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.

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 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.

Study M13-545:
Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of

upadacitinib 7.5 mg QD (for subjects in Japan only), and 15 mg QD, and 30 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 M16-098:
Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with AS who have completed Period 1.

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 DB 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 DB 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 DB Period.