PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]RINVOQ®

Upadacitinib extended-release tablets

Extended-release tablets, 15 mg upadacitinib, oral

Extended-release tablets, 30 mg upadacitinib, oral

Extended-release tablets, 45 mg upadacitinib, oral

Selective immunosuppressant

AbbVie Corporation

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St-Laurent, QC H4S 1Z1

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RECENT MAJOR LABEL CHANGES

1 Indications	10/2023
1.1 Indications, Pediatrics	10/2023
3 Serious Warnings and Precautions Box	07/2022
4.1 Dosage and Administration, Dosing Considerations	10/2023
4.2 Dosage and Administration, Recommended Dose and Dosage Adjustment	10/2023
4.4 Dosage and Administration, Administration	10/2023
7 Warnings and Precautions	10/2023
7 Warnings and Precautions, 7.1.3 Pediatrics	10/2023
7 Warnings and Precautions, 7.1.4 Geriatrics	10/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Rheumatoid Arthritis

RINVOQ (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.

RINVOQ may be used as monotherapy or in combination with methotrexate.

Axial Spondyloarthritis (axSpA)

Ankylosing Spondylitis (AS, radiographic axial spondyloarthritis)

RINVOQ is indicated for the treatment of adults with active ankylosing spondylitis who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable.

RINVOQ may be used as monotherapy or in combination with nonsteroidal anti-inflammatory drugs (NSAIDs).

Non-radiographic Axial Spondyloarthritis (nr-axSpA)

RINVOQ is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response to a biologic DMARD or when use of those therapies is inadvisable.

RINVOQ may be used as monotherapy or in combination with NSAIDs.

Atopic Dermatitis

RINVOQ is indicated for the treatment of adults and adolescents 12 years of age and older with refractory moderate to severe atopic dermatitis (AD) who are not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.

RINVOQ can be used with or without topical corticosteroids.

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional, and/or biologic therapy.

Crohn's Disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional and/or biologic therapy.

Limitations of Use

RINVOQ should not be used in combination with other Janus kinase (JAK) inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine, 6-mercaptopurine and cyclosporine (see **7 WARNINGS AND PRECAUTIONS**).

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 18 years with rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ulcerative colitis or Crohn's disease have not yet been established. No data are available; therefore, RINVOQ should not be used in this pediatric population (see **4.2 Recommended Dose and Dosage Adjustment**, **7.1.3 Pediatrics**, and **10.3 Pharmacokinetics**).

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of RINVOQ in pediatric patients 12-17 years of age, weighing ≥ 40 kg has been established for the treatment of refractory moderate to severe atopic dermatitis not adequately controlled with a systemic treatment (e.g., steroid or biologic) or when use of those therapies is inadvisable.

The safety and efficacy of RINVOQ in adolescents weighing < 40 kg and in children aged 0 to less than 12 years with atopic dermatitis have not yet been established. No data are available; therefore, RINVOQ should not be used in this pediatric patient population (see **4.2 Recommended Dose and Dosage Adjustment**, **7.1.3 Pediatrics**, and **10.3 Pharmacokinetics**).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Caution should be used when treating geriatric patients with RINVOQ. There are limited data in patients 75 years of age and older. In clinical studies of patients treated with RINVOQ, there was an increased incidence of adverse events, including serious infections, in patients 65 years of age and older (see **4.2 Recommended Dose and Dosage Adjustment**, **7.1.4 Geriatrics**, and **10.3 Pharmacokinetics**).

2 CONTRAINDICATIONS

RINVOQ is contraindicated in patients who are hypersensitive to upadacitinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death (see **7 WARNINGS AND PRECAUTIONS** and **8.2 Clinical Trial Adverse Reactions**). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment

for latent infection should be considered prior to RINVOQ use.

- Invasive fungal infections, including cryptococcosis and pneumocystosis.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

Treatment with RINVOQ should not be initiated in patients with active infections including chronic or localized infections.

The risks and benefits of treatment with RINVOQ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy (see **7 WARNINGS AND PRECAUTIONS**).

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. An increase in malignancies, including lung cancer, were observed in rheumatoid arthritis (RA) patients 50 years or older with at least one additional cardiovascular (CV) risk factor who were taking a different JAK inhibitor, compared with tumour necrosis factor (TNF) inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors (see **7 WARNINGS AND PRECAUTIONS**).

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including RINVOQ, for inflammatory conditions. Many of these adverse events were serious and some resulted in death. RA patients 50 years or older with at least one additional CV risk factor had a higher rate of all-cause mortality and thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Consider the risks and benefits prior to treating patients who may be at increased risk for thrombosis. Discontinue RINVOQ and promptly evaluate patients with symptoms of thrombosis (see **7 WARNINGS AND PRECAUTIONS**).

MAJOR ADVERSE CARDIOVASCULAR EVENTS

Major adverse cardiovascular events, including non-fatal myocardial infarction, were observed more frequently in RA patients 50 years or older with at least one additional CV risk factor in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other CV risk factors (see **7 WARNINGS AND PRECAUTIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- RINVOQ should not be initiated in patients with active infections including chronic or localized infections (see **7 WARNINGS AND PRECAUTIONS**).
- RINVOQ should not be initiated in patients with an absolute lymphocyte count (ALC) less than 0.5 x 10^9 cells/L, absolute neutrophil count (ANC) less than 1 x 10^9 cells/L, or hemoglobin level less than 80 g/L (see **7 WARNINGS AND PRECAUTIONS**).
- RINVOQ should not be initiated in patients with severe hepatic impairment (Child-Pugh C) (see **10.3 Pharmacokinetics**).
- RINVOQ should not be used concomitantly with other potent systemic immunosuppressants. Concomitant use of RINVOQ with other potent immunosuppressants (such as azathioprine, cyclosporine, tacrolimus), biologic DMARDs, or other JAK inhibitors has not been evaluated in clinical studies. There is a risk of additive immunosuppression when RINVOQ is co-administered with potent immunosuppressant drugs (see **7 WARNINGS AND PRECAUTIONS** and **9.4 Drug-Drug Interactions**).
- RINVOQ 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A inhibitors. RINVOQ 30 mg once daily is not recommended for patients receiving chronic treatment with strong CYP3A4 inhibitors. For patients with ulcerative colitis using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily (for up to 8 weeks) and the recommended maintenance dose is 15 mg once daily. For patients with Crohn's disease using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily (for up to 12 weeks) and the recommended maintenance dose is 15 mg once daily. Upadacitinib exposure is increased when co-administered with strong CYP3A inhibitors (such as ketoconazole and clarithromycin) (see **9.2 Drug Interactions Overview**).
- Co-administration of RINVOQ with strong CYP3A4 inducers is not recommended. Upadacitinib exposure is decreased when co-administered with strong CYP3A inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ (see **7 WARNINGS AND PRECAUTIONS** and **9.2 Drug Interactions Overview**).
- RINVOQ 15 mg once daily is the recommended dose for patients with severe renal impairment. No dose adjustment is required in patients with mild or moderate renal impairment (see **10.3 Pharmacokinetics**).

4.2 Recommended Dose and Dosage Adjustment

Note: See **Table 1** for the summary of the recommended dose for each indication.

Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis

The recommended oral dose of RINVOQ is 15 mg once daily.

Atopic Dermatitis

Adults

The recommended starting dose of RINVOQ is 15 mg once daily. If an adequate response (e.g., EASI 75) is not achieved, consider increasing dosage to 30 mg once daily. For some patients, such as those with severe disease, a starting dose of 30 mg once daily may be appropriate. Discontinue RINVOQ if an adequate response is not achieved with the 30 mg dose after 16 weeks of treatment. Use the lowest effective dose needed to maintain response.

For patients ≥ 65 years of age, the only recommended maintenance dose is 15 mg once daily. The 30 mg dose once daily is not recommended in these patients.

Adolescents (from 12 to 17 years of age)

The recommended dose of RINVOQ is 15 mg once daily for adolescents weighing at least 40 kg.

RINVOQ has not been studied in adolescents weighing less than 40 kg.

Ulcerative Colitis

Induction

The recommended induction dose is RINVOQ 45 mg once daily for 8 weeks.

Maintenance

The recommended dose for maintenance treatment is RINVOQ 15 mg once daily. For some patients, such as those with refractory, severe, or extensive disease, a maintenance dose of 30 mg once daily may be appropriate. Use the lowest effective dose needed to maintain response. Discontinue treatment if response is not maintained with the 30 mg dose.

For patients ≥ 65 years of age, the only recommended maintenance dose is 15 mg once daily. The 30 mg dose once daily is not recommended in these patients.

In patients who have responded to treatment with RINVOQ, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Crohn's Disease

Induction

The recommended induction dose of RINVOQ is 45 mg once daily for 12 weeks.

Maintenance

The recommended dose of RINVOQ for maintenance treatment is 15 mg or 30 mg once daily based on patient presentation.

- A dose of 30 mg once daily may be appropriate for patients with high disease burden (such as refractory or severe disease) or those who do not show adequate therapeutic benefit with 15 mg once daily.
- The lowest effective dose for maintenance should be used.

For patients ≥ 65 years of age, the recommended maintenance dose is 15 mg once daily.

In patients who are responding to induction or maintenance treatment with RINVOQ, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Table 1. Recommended dose of RINVOQ

Indication	Age	Indicated Dose
Rheumatoid Arthritis	Adults 18 years of age or older	15 mg once daily
Psoriatic Arthritis	Adults 18 years of age or older	15 mg once daily
Axial Spondyloarthritis	Adults 18 years of age or older	15 mg once daily
Atopic Dermatitis	Adolescents 12 to 17 years of age ≥ 40 kg	15 mg once daily
	Adults 18 to 64 years of age	15 mg or 30 mg once daily[a]
	Adults ≥ 65 years of age	15 mg once daily
Ulcerative Colitis		
Induction	Adults 18 years of age or older	45 mg once daily for 8 weeks
Maintenance	Adults 18 to 64 years of age	15 mg or 30 mg once daily[a]
	Adults ≥ 65 years of age	15 mg once daily
Crohn's Disease		
Induction	Adults 18 of age or older	45 mg once daily for 12 weeks
Maintenance	Adults 18 to 64 years of age	15 mg or 30 mg once daily[a]
	Adults ≥ 65 years of age	15 mg once daily

a. Use the 30 mg dose only in patients with severe disease or those who do not achieve an adequate response with the 15 mg dose. Consider the benefit-risk of using RINVOQ 30 mg prior to use (see **7 WARNINGS AND PRECAUTIONS**).

Dose Interruption

RINVOQ treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see **7 WARNINGS AND PRECAUTIONS**).

RINVOQ treatment should be interrupted for management of laboratory abnormalities as described in **Table 2**.

Table 2. Laboratory measures and monitoring guidance

Laboratory measure	Action	Monitoring guidance
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1 x 10^9 cells/L and may be restarted once ANC returns above this value	Evaluate at baseline and then no later than 12 weeks after initiation of treatment. Thereafter evaluate according to individual patient management.
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is < 0.5 x 10^9 cells/L and may be restarted once ALC returns above this value	
Hemoglobin (Hb)	Treatment should be interrupted if Hb is < 80 g/L and may be restarted once Hb returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	Evaluate at baseline and thereafter according to routine patient management.
Lipids	Patients should be managed according to international clinical guidelines for hyperlipidemia	Evaluate at baseline and 12 weeks after initiation of treatment. Thereafter evaluate according to international clinical guidelines for hyperlipidemia.

Dosing in Special Populations

Pediatrics (< 18 years of age):

Atopic Dermatitis: In adolescents 12 to 17 years of age ≥ 40 kg, RINVOQ is indicated as 15 mg once daily.

The safety and efficacy of RINVOQ in adolescents weighing < 40 kg and in children aged 0 to less than 12 years have not yet been established. No data are available; therefore, RINVOQ should not be used in this pediatric patient population (see **1.1 Pediatrics**, **7.1.3 Pediatrics**, and **10.3 Pharmacokinetics**).

Rheumatoid Arthritis, Psoriatic Arthritis, Axial Spondyloarthritis, Ulcerative Colitis or Crohn's Disease: Health Canada has not authorized an indication for pediatric use of RINVOQ. No data are available regarding the safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 18 years. Therefore, RINVOQ should not be used in this pediatric patient population (see **1.1 Pediatrics**, **7.1.3 Pediatrics**, and **10.3 Pharmacokinetics**).

Geriatric (≥ 65 years of age): Rheumatoid Arthritis, Psoriatic Arthritis, Axial Spondyloarthritis, Atopic Dermatitis, Ulcerative Colitis (maintenance treatment phase) or Crohn's Disease (maintenance treatment phase): RINVOQ 15 mg once daily is the only recommended dose in patients aged 65 years and older. No dose adjustment is required (see **7.1.4 Geriatrics** and **10.3 Pharmacokinetics**).

Hepatic Impairment: RINVOQ should not be used in patients with severe hepatic impairment (Child-Pugh C). The use of RINVOQ has not been studied in patients with severe hepatic impairment. No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see **10.3 Pharmacokinetics**).

Renal Impairment: No dose adjustment is required in patients with mild or moderate renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease (see **10.3 Pharmacokinetics**).

For patients with severe renal impairment, the following dose adjustments are recommended:

Table 3. Recommended Dose for Severe Renal Impairment

	Indication	Recommended once daily dose
Severe renal impairment	Rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and Axial Spondyloarthritis	15 mg
	Ulcerative Colitis, Crohn's Disease	Induction: 30 mg
		Maintenance: 15 mg

4.3 Reconstitution

No reconstitution required.

4.4 Administration

RINVOQ is to be taken orally once daily with or without food and may be taken at any time of the day. RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

Rheumatoid Arthritis

RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Psoriatic Arthritis

RINVOQ may be used as monotherapy or in combination with methotrexate.

Axial Spondyloarthritis

RINVOQ may be used as monotherapy or in combination with NSAIDs.

Atopic Dermatitis

Concomitant Topical Therapies: RINVOQ can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas.

Ulcerative Colitis and Crohn's Disease

RINVOQ may be used as monotherapy or in combination with conventional therapy.

4.5 Missed Dose

If a dose of RINVOQ is missed and it is more than 10 hours from the next scheduled dose, advise the patient to take a dose as soon as possible and then to take the next dose at the usual time. If a dose is missed and it is less than 10 hours from the next scheduled dose, advise the patient to skip the missed dose and take only a single dose as usual the following day. Advise the patient not to double a dose to make up for a missed dose.

5 OVERDOSAGE

Upadacitinib was administered in clinical trials up to doses equivalent in daily AUC (area under the curve) to 60 mg extended-release once daily. Adverse events were comparable to those seen at lower doses and no specific toxicities were identified. Approximately 90% of upadacitinib in the systemic circulation is eliminated within 24 hours of dosing (within the range of doses evaluated in clinical studies). In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	extended-release tablet/ 15 mg/upadacitinib	black iron oxide (E172)/ferrosoferric oxide, hypromellose, iron oxide red (E172), macrogol/polyethylene glycol, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, silica (colloidal anhydrous)/colloidal silicon dioxide, talc, tartaric acid, and titanium dioxide (E171)
oral	extended-release tablet/ 30 mg/upadacitinib	hypromellose, iron oxide red (E172), macrogol/polyethylene glycol, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, silica (colloidal anhydrous)/colloidal silicon dioxide, talc, tartaric acid, and titanium dioxide (E171)
oral	extended-release tablet/ 45 mg/upadacitinib	hypromellose, iron oxide red (E172), iron oxide yellow (E172), macrogol/polyethylene glycol, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, silica (colloidal anhydrous)/colloidal silicon dioxide, talc, tartaric acid, and titanium dioxide (E171).

RINVOQ 15 mg extended-release tablets are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side. The tablets are provided in bottles. Each bottle contains 30 tablets.

RINVOQ 30 mg extended-release tablets are red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a30' on one side. The tablets are provided in bottles. Each bottle contains 30 tablets.

RINVOQ 45 mg extended-release tablets are yellow biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a45' on one side. The tablets are provided in bottles. Each bottle contains 28 tablets.

The tablets do not contain gluten.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

Carcinogenesis and Mutagenesis

Lymphoma and other malignancies were observed in clinical studies of RINVOQ (see **8.2 Clinical Trial Adverse Reactions**). A higher rate of malignancies, including NMSC, was observed with RINVOQ 30mg compared to RINVOQ 15 mg.

In a large randomized active-controlled study in RA patients 50 years and older with at least one additional CV risk factor, an increased incidence of malignancy, particularly lung cancer, lymphoma and NMSC, was observed with a different JAK inhibitor compared to TNF inhibitors. Patients who were 65 years and older, and current or past smokers were at additional increased risk.

Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in geriatric patients, patients who are current or past smokers, patients with a known malignancy other than a successfully treated NMSC or when considering continuing RINVOQ in patients who develop a malignancy.

Non-Melanoma Skin Cancer (NMSC): NMSC is a dose-related adverse reaction, with a greater risk of occurrence and reoccurrence in patients treated with 30 mg RINVOQ than in patients treated with 15 mg RINVOQ. An increase in NMSC was observed in patients treated with RINVOQ compared to TNF inhibitors. Caution should be used when treating patients with a prior history of NMSC. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Cardiovascular

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ (see **8.2 Clinical Trial Adverse Reactions**). Many of these adverse events were serious and some resulted in death.

In a large, randomized, active-controlled study in RA patients 50 years of age and older with at least one additional CV risk factor, a dose dependent increased incidence of venous thromboembolic events (VTE) was observed with a different JAK inhibitor compared with TNF inhibitors.

Consider the risks and benefits of RINVOQ treatment prior to treating patients who may be at increased risk of thrombosis. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, current or history of smoking, obesity, a medical history of DVT/PE, prothrombotic disorder, use of combined hormonal contraceptives or hormone replacement therapy, patients undergoing major surgery, or prolonged immobilization. If clinical features of DVT/PE occur, RINVOQ treatment should be discontinued, and patients should be evaluated promptly and treated appropriately.

Major Adverse Cardiovascular Events: In a large, randomized, active-controlled study in RA patients 50 years of age and older with at least one additional CV factor, an increased incidence of major adverse cardiovascular events (MACE: non-fatal myocardial infarction [MI], non-fatal stroke, and CV deaths excluding PE) was observed with a different JAK inhibitor compared with TNF inhibitors. This increase in MACE was primarily due to an increased incidence of non-fatal MI.

Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in geriatric patients, patients who are current or past smokers, and patients with other CV risk factors, or when considering continuing RINVOQ in patients who develop MACE.

Endocrine and Metabolism

Lipids: Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed at baseline, 12 weeks after initiation of RINVOQ treatment and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**)

Gastrointestinal

Gastrointestinal Perforations: Events of gastrointestinal perforation have been reported in clinical studies with RINVOQ (see **8.2 Clinical Trial Adverse Reactions**), and from post-marketing sources.

RINVOQ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with diverticular disease, a history of diverticulitis, or who are taking NSAIDs, corticosteroids or opioids). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Hematologic

Anemia: Decreases in hemoglobin levels to less than 80 g/L were reported in RINVOQ clinical studies (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Evaluate hemoglobin prior to initiation of RINVOQ and thereafter according to routine patient management. Do not initiate RINVOQ treatment, and interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 80 g/L) (see **4.1 Dosing Considerations** and **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**)

Lymphopenia: Absolute Lymphocyte Counts (ALC) less than 0.5 x 10^9 cells/L were reported in RINVOQ clinical studies (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Evaluate lymphocyte counts prior to initiation of RINVOQ and thereafter according to routine patient management. Do not initiate RINVOQ treatment, and interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 0.5 x 10^9 cells/L) (see **4.1 Dosing Considerations**, and **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Neutropenia: Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1 x 10^9 cells/L) (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Evaluate neutrophil counts prior to initiating RINVOQ and thereafter according to routine patient management. Do not initiate RINVOQ treatment, and interrupt RINVOQ

treatment in patients with a low neutrophil count (i.e., ANC less than 1 x 10^9 cells/L) (**4.1 Dosing Considerations**, **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Hepatic/Biliary/Pancreatic

Treatment with RINVOQ was associated with an increased incidence of liver enzyme elevation compared to placebo (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Increases to ≥ 3X the upper limit of normal (ULN) for both alanine transaminase (ALT) and aspartate transaminase (AST) were the more frequently reported, but increases to ≥ 5X and ≥ 10X ULN were also observed in patients treated with RINVOQ in clinical trials. Unconfirmed drug induced liver injury (DILI) was observed in four patients receiving upadacitinib in clinical trials, including 2 patients receiving RINVOQ. Upadacitinib was discontinued in 3 cases and was continued without interruption in one patient receiving RINVOQ.

Liver enzymes should be evaluated before initiating RINVOQ treatment and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of DILI. If increases in ALT or AST are observed during routine patient management and DILI is suspected, RINVOQ should be interrupted until this diagnosis is excluded (see **4.2 Recommended Dose and Dosage Adjustment** and **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**).

Although patients with active hepatitis B or C infection were excluded from clinical trials, cases of hepatitis B virus reactivation were still reported in patients enrolled in the clinical studies of RINVOQ. Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**).

The use of RINVOQ has not been studied in patients with severe hepatic impairment and therefore, RINVOQ should not be used in these patients (see **4.2 Recommended Dose and Dosage Adjustment** and **10.3 Pharmacokinetics**).

Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy (see **8 ADVERSE REACTIONS**).

Immune

RINVOQ should not be used concomitantly with other potent immunosuppressants. Concomitant use of RINVOQ with other potent immunosuppressants (such as azathioprine, cyclosporine, tacrolimus), biologic DMARDs, or other JAK inhibitors has not been evaluated in clinical studies. There is a risk of additive immunosuppression when RINVOQ is co-administered with potent immunosuppressant drugs (see **4.1 Dosing Considerations** and **9.2 Drug Interactions Overview**).

Immunizations

No data are available on the response to vaccination with live vaccines in patients receiving RINVOQ. Live or attenuated vaccines should not be used immediately prior to or during RINVOQ therapy. Prior to initiating RINVOQ treatment, patients should be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines. The interval

between live vaccinations and initiation of RINVOQ therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Individuals taking RINVOQ may have a reduced antibody response to non-live vaccines (see **10.2 Pharmacodynamics**).

Infections

Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis (see **8.2 Clinical Trial Adverse Reactions**). Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis were reported with RINVOQ. A higher rate of serious infections was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

RINVOQ should not be initiated in patients with active infections including chronic or localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

- With chronic or recurrent infection
- Who have been exposed to tuberculosis
- With a history of a serious or an opportunistic infection
- Who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- With underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with RINVOQ 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 RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. Do not resume RINVOQ treatment until the infection is controlled.

Tuberculosis: Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

Monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical studies with RINVOQ (see **8.2 Clinical Trial Adverse Reactions**). If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies. However, cases of hepatitis B reactivation were still reported in patients enrolled in the clinical studies

of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Monitoring and Laboratory Tests

Hematology: Lymphocyte counts, neutrophil counts, and hemoglobin should be evaluated before initiating RINVOQ treatment and thereafter according to routine patient management. Treatment should not be initiated and should be interrupted in patients with low lymphocyte count (ALC less than 0.5 x 10^9 cells/L), low neutrophil count (ANC less than 1 x 10^9 cells/L), or low hemoglobin level (less than 80 g/L) (see **4.1 Dosing Considerations**, **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Lipids: Assessment of lipid parameters should be performed at baseline, 12 weeks after initiation of RINVOQ treatment and thereafter according to the clinical guidelines for hyperlipidemia. Patients should be managed according to clinical guidelines for the management of hyperlipidemia (see **4.2 Recommended Dose and Dosage Adjustment** and **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**).

Liver Enzyme Elevations: Liver enzymes should be evaluated before initiating RINVOQ treatment and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ treatment should be interrupted until this diagnosis is excluded (see **4.2 Recommended Dose and Dosage Adjustment** and **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**).

Musculoskeletal

Treatment with RINVOQ was associated with dose-related increases in creatine phosphokinase (CPK) (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). CPK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis.

Reproductive Health: Female and Male Potential

Teratogenic Risk: Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations (see **16 NON-CLINICAL TOXICOLOGY**). Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy (see **7.1.1 Pregnant Women**).

7.1 Special Populations

7.1.1 Pregnant Women

RINVOQ should not be used during pregnancy. There are limited human data on the use of upadacitinib in pregnant women. There are no adequate and well-controlled studies to assess the use of RINVOQ in pregnant women. Studies in animals have shown reproductive toxicity (see **16 NON-CLINICAL TOXICOLOGY**) In animal embryo-fetal developmental studies, upadacitinib was teratogenic in rats and rabbits with dose-related increases in skeletal malformations in rat fetuses and an increased incidence of cardiovascular malformations in rabbit fetuses when exposed in utero. Increased post-implantation loss was seen in rabbits and decreased fetal body weights were observed in both rats and rabbits. The

effect of upadacitinib on human fertility has not been evaluated. Animal studies do not indicate effects with respect to fertility (see **16 NON-CLINICAL TOXICOLOGY**).

Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus and may cause embryo-fetal harm when administered to pregnant women. Women of reproductive potential should be advised to use effective contraception during treatment and for 4 weeks following the final dose of RINVOQ. If the patient becomes pregnant while taking RINVOQ, inform the patient of the potential hazard to a fetus.

7.1.2 Breast-feeding

RINVOQ should not be used during breast-feeding. It is unknown if upadacitinib is excreted in human milk. Lactation studies have not been conducted to assess the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/ toxicological data in animals have shown excretion of upadacitinib in milk. Following administration of upadacitinib to lactating rats, upadacitinib exposure was approximately 30-fold greater in milk than in maternal plasma. Approximately 97% of drug-related material in milk was parent drug.

A risk to newborns/infants cannot be excluded. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, patients should be advised not to breast-feed during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age):

Atopic Dermatitis: A total of 344 adolescents aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across the three Phase 3 studies to receive either 15 mg (N = 114) or 30 mg (N = 114) RINVOQ or matching placebo (N = 116) in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the adolescents and adults (see **14.1 Clinical Trials by Indication**). The adverse event profile in adolescents was generally similar to the adults.

Safety and efficacy of RINVOQ in patients less than 12 years of age with atopic dermatitis have not been established.

Rheumatoid Arthritis, Psoriatic Arthritis, Axial Spondyloarthritis, Ulcerative Colitis, or Crohn's Disease: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **1.1 Pediatrics**, **4.2 Recommended Dose and Dosage Adjustment**, and **10.3 Pharmacokinetics**).

7.1.4 Geriatrics

Caution should be used when treating geriatric patients with RINVOQ. There are limited data in patients 75 years of age and older.

Rheumatoid Arthritis: In five Phase 3 clinical studies, 518 rheumatoid arthritis patients treated with RINVOQ were 65 years of age and older, including 78 patients 75 years of age and older.

Psoriatic Arthritis: In two Phase 3 clinical studies, 129 psoriatic arthritis patients treated with RINVOQ were 65 years of age or older, including 18 patients 75 years of age and older. Although no differences in effectiveness were observed between these patients and younger patients, there was an increased incidence of adverse events, including serious infections and adverse events leading to RINVOQ

discontinuation in patients ≥ 65 years of age (see **1.2 Geriatrics**, **4.2 Recommended Dose and Dosage Adjustment**, and **10.3 Pharmacokinetics**).

Axial Spondyloarthritis

- Ankylosing Spondylitis: In two Phase 3 clinical studies, 32 ankylosing spondylitis patients treated with RINVOQ were 65 years of age or older, including 4 patients 75 years of age or older.
- Non-radiographic Axial Spondyloarthritis: In one Phase 3 clinical study, a total of 9 non-radiographic axial spondyloarthritis patients were 65 years of age or older.

Atopic Dermatitis: In three Phase 3 clinical studies, 115 atopic dermatitis patients treated with RINVOQ were 65 to 75 years of age at study entry. In the elderly, a higher rate of overall adverse events was observed compared to younger patients and in the RINVOQ 30 mg dose group compared to the 15 mg dose group. The use of 30 mg in patients over 65 years of age is not recommended.

Ulcerative Colitis: Of the 576 patients who responded to RINVOQ 45 mg once daily induction treatment and received maintenance treatment in the ulcerative colitis studies, 52 patients were 65 years of age or older. In the elderly patients, a higher rate of overall adverse events was observed compared to younger patients and in the RINVOQ 30 mg once daily dose group compared to the RINVOQ 15 mg once daily dose group. The use of 30 mg for maintenance in patients over 65 years of age is not recommended.

Crohn's Disease: Of the 673 patients who responded to RINVOQ 45 mg induction treatment and received maintenance treatment in the phase 3 clinical studies, 23 patients were 65 years of age or older. A higher rate of overall adverse events was observed in the elderly with RINVOQ 30 mg compared to younger patients and RINVOQ 15 mg dose.

7.1.5 Asian Patients

Asian patients have an increased risk of herpes zoster compared to other races. Therefore, RINVOQ should be used with caution in these patients (see **8 ADVERSE REACTIONS**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis

The most commonly reported adverse reactions occurring in ≥ 2% of patients treated with RINVOQ 15 mg were upper respiratory tract infection, nausea, bronchitis, blood creatine phosphokinase (CPK) increased, urinary tract infection, ALT increased, AST increased, neutropenia, headache, cough and back pain. There is increased incidence of opportunistic infections including herpes zoster in patients taking RINVOQ. A higher incidence of herpes zoster was observed in Asian patients. Therefore, RINVOQ should be used with caution in Asian patients.

In clinical trials, the most common SAEs in patients treated with upadacitinib (incidence rate of ≥ 0.5 per 100 patient-years) included pneumonia, osteoarthritis, and pulmonary embolism. Uncommon SAEs in patients treated with upadacitinib include deep vein thrombosis, arterial thrombosis, gastrointestinal perforation, anemia, malignancies, and cellulitis.

The most common causes of death in the upadacitinib clinical program were cardiovascular related.

The most common adverse reactions leading to discontinuation from treatment were infections. The most common infections (incidence rate of ≥ 0.5 per 100 patient-years) resulting in discontinuation of

treatment were pneumonia and herpes zoster [see **7 WARNINGS AND PRECAUTIONS**, **8.2 Clinical Trial Adverse Reactions**, **8.3 Less Common Clinical Trial Adverse Reactions**, **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**].

Atopic Dermatitis

In the placebo-controlled atopic dermatitis clinical trials, the most commonly reported adverse reactions (≥ 2% of patients) with RINVOQ 15 mg or 30 mg were upper respiratory tract infection (25.4%), acne (15.1%), herpes simplex (8.4%), headache (6.3%), CPK increased (5.5%), cough (3.2%), folliculitis (3.2%), abdominal pain (2.9%), nausea (2.7%), neutropenia (2.3%), pyrexia (2.1%), and influenza (2.1%).

The most common serious adverse reactions were serious infections.

The safety profile of upadacitinib with long-term treatment was generally consistent with the safety profile during the placebo-controlled period.

The safety profile in adolescents was generally similar to that in adults, with dose dependent increases in the rate of some adverse events, including neutropenia and herpes zoster. At both doses, the rate of neutropenia was slightly increased in adolescents compared to adults. The rate of herpes zoster in adolescents at the 30 mg dose was comparable to that in adults.

Ulcerative Colitis

In the placebo-controlled ulcerative colitis clinical trials, the most commonly reported adverse reactions (≥ 2% of patients) with induction dose of RINVOQ 45 mg were upper respiratory tract infection (8.3%), acne (6.3%), blood CPK increased (5.1%), neutropenia (4.6%), rash (3.5%), lymphopenia (2.5%), pyrexia (2.5%), folliculitis (2.2%) and herpes simplex (2.1%). With maintenance dose of RINVOQ 15 mg or 30 mg, the most commonly reported adverse reactions (≥ 2% of patients) were upper respiratory tract infection (19.9%), blood CPK increased (7.6%), neutropenia (6.0%), rash (5.2%), herpes zoster (4.4%), hypercholesterolemia (4.0%), AST increased (3.6%), folliculitis (3.6%), influenza (3.2%), and herpes simplex (3.2%), ALT increased (2.8%), and hyperlipidemia (2.4%).

The most common serious adverse reactions were serious infections.

The safety profile of upadacitinib with long-term treatment was generally consistent with the safety profile during the placebo-controlled periods.

Overall, the safety profile observed in patients with ulcerative colitis was consistent with the safety profiles in other indications.

Crohn's Disease

The most commonly reported adverse reactions occurring in ≥ 2% of patients treated with RINVOQ 45 mg, 30 mg, or 15 mg in the induction and maintenance clinical trials were upper respiratory tract infection (14.9%), pyrexia (8.7%), anemia (7.4%), headache (6.6%), acne (6.2%), herpes zoster (6.1%), blood CPK increased (4.1%), pneumonia (4.1%), bronchitis (3.9%), aspartate transaminase increased (3.9%), fatigue (3.9%), alanine transaminase increased (3.5%), influenza (3.0%), herpes simplex (2.7%), and neutropaenia (2.2%).

The most common SAEs and AEs leading to discontinuation from treatment in Crohn's disease patients treated with RINVOQ were worsening of Crohn's disease.

Overall, the safety profile observed in patients with Crohn's disease treated with RINVOQ was consistent with the known safety profile of RINVOQ.

In subjects taking RINVOQ 30 mg in the maintenance and open label extension studies of the Phase 3 clinical trial program, thromboses and gastrointestinal perforations were observed. (See **8.2 Clinical Trial Adverse Reactions**, **Table 11**)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions; therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Rheumatoid Arthritis

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical studies, of whom 2806 were exposed to upadacitinib for at least one year.

In five Phase 3 studies, 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In Studies I, II, III and V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of whom 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of whom 946 were exposed for at least one year.

The following four safety datasets were integrated from the five Phase 3 clinical studies and were used to evaluate the adverse drug reaction profile of RINVOQ 15 mg once daily (QD):

1) Placebo-controlled studies: Studies III, IV, and V were integrated to represent the safety of RINVOQ 15 mg (n = 1035) in comparison to placebo (n = 1042) for up to 12 to 14 weeks following treatment initiation.
2) Studies III and V were integrated to represent safety through 12 weeks for placebo (n = 390), RINVOQ 15 mg (n = 385), and upadacitinib 30 mg (n = 384). Study IV did not include the 30 mg dose and therefore, safety data for upadacitinib 30 mg can only be compared to placebo and RINVOQ 15 mg data from pooling Studies III and V.
3) Methotrexate (MTX)-controlled studies: Studies I and II were integrated to represent safety through 12 to 14 weeks for MTX (n = 530), RINVOQ 15 mg (n = 534), and upadacitinib 30 mg (n = 529).
4) 12-Month exposure dataset: Studies I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n = 1213) and upadacitinib 30 mg (n = 1203).

Exposure adjusted incidence rates were adjusted by study for all the adverse events (AEs) reported.

The adverse reactions occurring in ≥ 1% of patients treated with RINVOQ 15 mg once daily during the double-blind, placebo-controlled portion of the three placebo-controlled studies (Studies III, IV, and V) for up to 12 to 14 weeks are listed below in **Table 5**.

Table 5. Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Studies

	Placebo N = 1042 (%)	RINVOQ 15 mg N = 1035 (%)	Adalimumab[a] N = 327 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5	8.0
Nausea	2.2	3.5	2.4
Blood creatine phosphokinase (CPK) increased	0.9	2.5	0.3
Cough	1.0	2.2	1.2
Neutropenia	0.2	1.8	0.3
Pyrexia	0	1.2	0.3
Hypercholesterolemia	0.2	1.1	1.2
Weight increased	0.3	1.0	0.3

a. Study IV

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

The frequency of herpes zoster, lymphopenia, CPK elevations and ALT/AST elevations were higher with RINVOQ 15 mg compared to adalimumab.

Specific Adverse Reactions

The exposure-adjusted rates of specific adverse reactions are provided in **Table 6**.

Table 6. Specific Adverse Reactions Reported in Rheumatoid Arthritis Patients in Clinical Trials with RINVOQ

	Placebo-controlled Studies Week 12/14 n (n/100 PY)			MTX-controlled Studies Week 12/14 n (n/100 PY)			12-month Exposure n (n/100 PY)	
	Placebo N= 1042	RINVOQ 15 mg N= 1035	Upadacitinib 30 mg N= 384	MTX N= 530	RINVOQ 15 mg N= 534	Upadacitinib 30 mg N= 529	RINVOQ 15 mg N= 1213	Upadacitinib 30 mg N= 1203
Infections	218 (95.7)	284 (127.8)	126 (180.3)	127 (119.5)	104 (91.8)	128 (115.1)	615 (83.8)	674 (99.7)
Serious Infections[a]	6 (2.3)	12 (4.6)	7 (8.2)	2 (1.6)	3 (2.4)	8 (6.4)	38 (3.5)	59 (5.6)
TB[b]	0	0	0	0	0	0	2 (0.2)	1 (< 0.1)
Opportunistic Infections (excluding TB)	3 (1.2)	5 (1.9)	6 (7.1)	1 (0.8)	0	4 (3.2)	7 (0.6)	15 (1.4)
Malignancy (excluding NMSC)	1 (0.4)	1 (0.4)	3 (3.5)	1 (0.8)	3 (2.4)	0	13 (1.2)	14 (1.3)
Gastrointestinal Perforations	0	0	0	0	0	2 (1.6)	1 (< 0.1)	4 (0.4)
Venous Thrombosis[c]	1 (0.4)	1 (0.4)	0	0[c]	1 (0.8)	1 (0.8)	5 (0.5)	4 (0.4)
Arterial Thrombosis[d]	0	0	0	0	0	0[d]	0	2 (0.2)

a. The most frequently reported serious infections were pneumonia and cellulitis.
b. Including extra-pulmonary tuberculosis.
c. One event of venous thrombosis was reported in MTX group between Week 12/14 and Week 24 (Study I).
d. One event of arterial thrombosis was reported in Upadacitinib 30 mg group between Week 12/14 and Week 24 (Study I).

Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical studies, of whom 722 were exposed to upadacitinib for at least one year. In the Phase 3 studies, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

Two placebo-controlled studies were integrated (640 patients on RINVOQ 15 mg once daily and 635 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 24 weeks after treatment initiation.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis.

During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were > 1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively, with placebo. A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

In patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy, higher rates were observed for serious infections (1.1% vs 0.5%, respectively), hepatic disorders (7.7% vs 4.2%, respectively), elevation of CPK (7.1% vs 5.2%, respectively), anemia (1.3% vs 0.5%, respectively), and lymphopenia (1.3% vs 1.1%, respectively).

Axial Spondyloarthritis

Ankylosing Spondylitis

A total of 596 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the two clinical studies representing 577.3 patient-years of exposure, of whom 228 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active ankylosing spondylitis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis and psoriatic arthritis.

During the 14-week placebo-controlled period in study AS-I, the frequency of increased CPK was 8.6% with RINVOQ 15 mg and 2.1% with placebo. During the 14-week placebo-controlled period in study AS-II the frequency of hyperuricemia was 2.8% with RINVOQ 15 mg and 0.5% with placebo.

Non-radiographic Axial Spondyloarthritis

A total of 187 patients with non-radiographic axial spondyloarthritis were treated with RINVOQ 15 mg in one clinical study representing 116.6 patient-years of exposure, of whom 35 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active non-radiographic axial spondyloarthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. No new safety findings were identified.

Atopic Dermatitis

A total of 2898 patients 12 years of age and older with atopic dermatitis were treated with upadacitinib in clinical studies, of whom 1920 were exposed to upadacitinib for at least one year. In the Phase 3 studies, 1239 patients received at least 1 dose of RINVOQ 15 mg, of whom 791 were exposed for at least one year and 1246 patients received at least 1 dose of RINVOQ 30 mg, of whom 826 were exposed for at least one year.

In the Phase 3 studies, 167 adolescents received at least 1 dose of RINVOQ 15 mg, of whom 110 were exposed for at least one year and 166 adolescents received at least 1 dose of RINVOQ 30 mg, of whom 113 were exposed for at least one year.

The adverse reactions occurring in ≥ 1% of patients treated with RINVOQ 15 mg or 30 mg once daily during the double-blind, placebo-controlled portion of the four global studies for up to 16 weeks are listed below in

Table 7.

Table 7. Adverse Reactions Reported in ≥ 1% of Atopic Dermatitis Patients Treated with RINVOQ 15 mg or 30 mg in Placebo-Controlled Studies

Adverse Reaction	Placebo N = 902 (%)	RINVOQ 15 mg N = 899 (%)	RINVOQ 30 mg N = 906 (%)
Upper respiratory tract infection (URTI)*	16.5	22.6	25.4

Adverse Reaction	Placebo N = 902 (%)	RINVOQ 15 mg N = 899 (%)	RINVOQ 30 mg N = 906 (%)
Acne	2.2	9.6	15.1
Herpes simplex**	1.7	4.1	8.4
Headache	4.3	5.6	6.3
Cough	1.4	3.2	3.0
Folliculitis	1.1	2.1	3.2
Abdominal pain***	0.8	2.9	2.3
Nausea	0.6	2.7	2.6
Pyrexia	1.0	1.7	2.1
Influenza	0.3	2.1	1.5
Weight increased	0.6	1.8	1.9
Fatigue	0.6	1.3	1.9
Herpes zoster	0.6	1.6	1.5
Urticaria	0.6	0.9	1.5

* Includes laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection

** Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes

*** Includes abdominal pain and abdominal pain upper

The safety profile of RINVOQ with long-term treatment was similar to the safety profile observed at Week 16.

Specific Adverse Reactions

The exposure-adjusted rates of specific adverse reactions are provided in **Table 8**.

Table 8. Specific Adverse Reactions Reported in Atopic Dermatitis Patients in Clinical Trials with RINVOQ

	Placebo-controlled Studies Week 16 n(n/100 PY)			Long-term Exposure n(n/100 PY)[d]	
	Placebo N = 902	RINVOQ 15 mg N = 899	RINVOQ 30 mg N = 906	RINVOQ 15 mg N = 1239	RINVOQ 30 mg N = 1246
Infections	271 (130.5)	348 (168.2)	390 (193.8)	642 (80.3)	711 (94.2)
Serious Infections[a]	5 (2.0)	7 (2.6)	4 (1.5)	26 (1.9)	30 (2.1)
TB[b]	0	0	0	1 (< 0.1)	1 (< 0.1)
Opportunistic Infections (excluding TB and herpes zoster)[c]	4 (1.6)	6 (2.2)	7 (2.6)	20 (1.5)	20 (1.4)
Herpes zoster	5 (2.0)	14 (5.2)	14 (5.2)	46 (3.4)	69 (5.0)

	Placebo-controlled Studies Week 16 n(n/100 PY)			Long-term Exposure n(n/100 PY)[d]	
	Placebo N = 902	RINVOQ 15 mg N = 899	RINVOQ 30 mg N = 906	RINVOQ 15 mg N = 1239	RINVOQ 30 mg N = 1246
Malignancy (excluding NMSC)	0	0	4 (1.5)	2 (0.1)	7 (0.5)
Gastrointestinal Perforations	0	0	0	0	0
Venous Thrombosis	1 (0.4)	0	0	1 (< 0.1)	1 (< 0.1)
Arterial Thrombosis	1 (0.4)	0	0	0	0

a. The most frequently reported serious infections were pneumonia.
b. Including extra-pulmonary tuberculosis.
c. All but one event was eczema herpeticum or Kaposi's varicelliform eruption.
d. Including global Phase 3 studies.

Ulcerative Colitis

RINVOQ has been studied in 1304 patients with moderately to severely active UC in one Phase 2b, three Phase 3 (UC-1, UC-2 and UC-3) randomized, double-blind, placebo-controlled clinical studies (see **14.1 Clinical Trials by Indication**), and a long-term extension study. A total of 721 patients were exposed to RINVOQ for at least one year.

In the induction studies (Phase 2b, UC-1, and UC-2), 719 patients received at least one dose of RINVOQ 45 mg, of whom 513 were exposed to 45 mg of RINVOQ QD for 8 weeks.

In the maintenance study UC-3 and the long-term extension study, 285 patients received at least one dose of RINVOQ 15 mg, of whom 131 were exposed for at least one year and 291 patients received at least one dose of RINVOQ 30 mg, of whom 137 were exposed for at least one year.

Induction Studies (Phase 2b, UC-1, UC-2)

Table 9. Adverse Reactions Reported in ≥1% of Ulcerative Colitis Patients Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies

Adverse Reaction	Placebo N = 378 n (%)	RINVOQ 45 mg N = 719 n (%)
Upper respiratory tract infection*	6.9	8.3
Acne*	1.3	6.3
Blood CPK increased	1.3	5.1
Neutropenia*	0.3	4.6
Rash*	0.8	3.5
Pyrexia	1.6	2.5
Lymphopenia*	0.5	2.5
Folliculitis	0.5	2.2
Herpes simplex*	0.3	2.1

*Presented as grouped term.

Maintenance Study (UC-3)

Table 10. Adverse Reactions Reported in ≥1% of Ulcerative Colitis Patients Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study[a]

	Placebo N = 245 (%)	RINVOQ 15 mg N = 250 (%)	RINVOQ 30 mg N = 251 (%)
Upper respiratory tract infection*	18.0	16.4	19.9
Blood CPK increased	2.0	5.6	7.6
Neutropenia*	2.0	2.8	6.0
Rash*	3.7	4.8	5.2
Herpes zoster*	0	4.4	4.0
Hypercholesterolemia*	0.8	2.4	4.0
Folliculitis	1.6	1.6	3.6
Influenza	1.2	2.8	3.2
Herpes simplex*	1.2	2.4	3.2
ALT increased	0.4	2.8	2.4
Hyperlipidemia*	0	2.4	2.4
AST increased	0.8	3.6	1.6

a. Upadacitinib 45 mg 8-week induction responders
*Presented as grouped term.

Table 11. Specific Adverse Reactions Reported in Ulcerative Colitis Patients in Clinical Trials with RINVOQ

	Placebo-Controlled Induction Week 8 n (n/100 PY)		Placebo-Controlled Maintenance Week 52 n (n/100 PY)			Long-Term Exposure[b] n (n/100 PY)	
	Placebo N= 378	RINVOQ 45 mg N= 719	Placebo N= 245	RINVOQ 15 mg N= 250	RINVOQ 30 mg N= 251	RINVOQ 15 mg N= 250	RINVOQ 30 mg N= 251
Infections	66 (129.4)	149 (152.3)	92 (97.2)	96 (70.2)	102 (71.8)	122 (59.9)	134 (69.0)
Serious Infections[a]	5 (9.0)	9 (8.2)	8 (6.4)	8 (4.5)	6 (3.0)	12 (3.9)	12 (4.0)
TB	0	0	0	0	0	0	0
Opportunistic Infections (excluding TB and herpes zoster)	1 (1.8)	3 (2.7)	2 (1.6)	2 (1.1)	1 (0.5)	2 (0.6)	1 (0.3)
Herpes Zoster	0	4 (3.6)	0	11 (6.2)	10 (5.1)	18 (6.1)	16 (5.5)
Malignancy (excluding NMSC)	0	0	1 (0.8)	1 (0.5)	2 (1.0)	1 (0.3)	3 (1.0)
Gastrointestinal Perforations	1 (1.8)	0	1(0.8)	0	0	0	0
Venous Thrombosis	1 (1.8)	1 (0.9)	0	2 (1.1)	2 (1.0)	3 (1.0)	2 (0.7)

[a] The most frequently reported serious infection in the ulcerative colitis studies was COVID-19 pneumonia.
[b] Events and exposure are inclusive of the maintenance period (52 Weeks) and long-term extension for patients remaining on the same dose.

Crohn's Disease

RINVOQ has been studied in patients with moderately to severely active Crohn's Disease (CD) in three Phase 3 (CD-1, CD-2, and CD-3) randomized, double-blind, placebo-controlled clinical studies (see **14 CLINICAL TRIALS**) with a total of 833 patients representing 1203 patient-years of exposure, of whom a total of 536 patients were exposed for at least one year.

In the induction studies (CD-1 and CD-2), 674 patients received at least one dose of RINVOQ 45 mg during the placebo-controlled period, of whom 592 were exposed for 12 weeks and 142 patients received at least one dose of RINVOQ 30 mg during the extended treatment period.

In the maintenance study CD-3, 221 patients received at least one dose of RINVOQ 15 mg, of whom 89 were exposed for at least one year and 229 patients received at least one dose of RINVOQ 30 mg, of whom 107 were exposed for at least one year.

Induction Studies (Phase 3, CD-1, CD-2)

Table 12. Adverse Reactions Reported in ≥ 1% of Patients with Crohn's Disease Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (CD-1 and CD-2)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N = 347 (%)	N = 674 (%)
Upper respiratory tract infection*	8.1	12.9
Anemia*	5.5	7.4
Acne*	1.7	6.2
Pyrexia	2.6	4.2
Increased blood creatine phosphokinase	1.2	3.0
Influenza	0.6	3.0
Herpes simplex*	1.2	2.7
Herpes zoster*	0	2.2
Neutropenia*	0.3	2.1
Folliculitis	0.3	1.3
Hypercholesterolemia*	0	1.0

* Presented as grouped term

Maintenance Study (Phase 3, CD-3)

Table 13. Adverse Reactions Reported in ≥ 1% of Patients with Crohn's Disease Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (CD-3)+

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	N = 223 (%)	N = 221 (%)	N = 229 (%)
Upper respiratory tract infection*	11.2	14.9	14.0
Pyrexia	2.7	6.8	8.7
Headache*	1.8	3.6	6.6
Herpes zoster*	2.2	4.1	6.1
Acne*	3.6	2.3	5.2
Increased blood creatine phosphokinase	1.8	4.1	3.9
Fatigue	2.2	3.6	3.9
Pneumonia*	0.4	4.1	1.7
Aspartate aminotransferase increased	0.4	1.4	3.9
Bronchitis*	0	1.4	3.9
Alanine aminotransferase increased	0	2.3	3.5
Neutropenia*	0.4	1.4	2.2
Hyperlipidemia*	0	1.8	0.9
Hypercholesterolemia*	0	1.8	0.4

+ Patients who were responders to 12 weeks induction therapy with RINVOQ 45 mg once daily

* Presented as grouped term

Specific Adverse Reactions

The exposure-adjusted rates of specific adverse reactions are provided in **Table 14**.

Table 14. Specific Adverse Reactions Reported in Crohn's Disease Patients in Clinical Trials with RINVOQ

	Induction Week 12 n (n/100 PY)		Maintenance Long-Term Exposure[b] n (n/100 PY)		
	Placebo N = 347	RINVOQ 45 mg N = 674	Placebo N = 223	RINVOQ 15 mg N = 221	RINVOQ 30 mg N = 229
Infections	68 (99.8)	205 (164.9)	71 (74.2)	94 (64.3)	107 (68.0)
Serious Infections[a]	6 (7.9)	13 (8.7)	10 (7.4)	7 (3.2)	13 (5.3)
TB	0	0	0	0	0
Opportunistic Infections (excluding TB)	0	2 (1.3)	0	1 (0.4)	1 (0.4)
Herpes Zoster	0	15 (10.0)	5 (3.7)	9 (4.2)	14 (5.7)
Malignancy (excluding NMSC)	0	0	1(0.7)	1 (0.4)	4 (1.5)
Gastrointestinal Perforations[c]	0	1 (0.7)	1 (0.7)	1 (0.4)	1 (0.4)
Venous Thrombosis[d]	0	0	0	0	1 (0.4)
Arterial Thrombosis[e]	0	0	0	0	0

a. The most frequently reported serious infection in the Crohn's disease studies was anal abscess.
b. Includes placebo-controlled maintenance (52-week) and long-term extension periods for patients remaining on the same dose.
c. Three placebo non responders who received 12-week RINVOQ 45 mg in the induction studies and 3 patients who received RINVOQ 30 mg as rescue therapy in the long-term extension study experienced gastrointestinal perforation.
d. Two patients who received RINVOQ 30 mg as rescue therapy in the long-term extension study experienced venous thrombosis (deep vein thrombosis and/or pulmonary embolism). One patient who received only placebo in the clinical studies experienced an event of deep vein thrombosis.
e. One patient who did not respond to RINVOQ 45 mg in the induction study and received RINVOQ 30 mg experienced an event of peripheral arterial thrombosis in the long-term extension study.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Adolescents with Atopic Dermatitis

A total of 343 adolescents aged 12 to 17 years weighing at least 40 kg with atopic dermatitis were treated in the Phase 3 studies. The safety profile for RINVOQ 15 mg was similar in adolescents and adults. The safety and efficacy of the 30 mg dose in adolescents are still being investigated. 30 mg is not approved for use in adolescents.

8.3 Less Common Clinical Trial Adverse Reactions

Rheumatoid Arthritis
Infections and Infestations: herpes zoster, herpes simplex, pneumonia, oral candidiasis.

Psoriatic Arthritis
The incidence rates of less common clinical trial adverse drug reactions (< 1%) in the two controlled Phase 3 psoriatic arthritis clinical studies were generally similar to those reported in RA clinical studies with the exception of herpes zoster, herpes simplex, and NMSC.

Atopic Dermatitis
Other adverse reactions (other than the adverse reactions listed in **Table 7**) reported in < 1% of patients in the RINVOQ 15 mg and/or 30 mg groups and at a higher rate than in the placebo group through Week 16 included oral candidiasis, pneumonia, and NMSC.

Ulcerative Colitis
Other adverse reactions reported in less than 1% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

Crohn's Disease

Other adverse reactions reported in less than 1% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 12 included bronchitis, pneumonia, oral candidiasis, and hyperlipidemia.

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg and/or 30 mg group and at a higher rate than in the placebo group through Week 52 included oral candidiasis and NMSC.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Rheumatoid Arthritis

Clinically significant changes in hematology and chemistry laboratory findings during the clinical trials are presented in **Table 15** and **Table 16**.

Table 15. Biochemical changes Reported in Rheumatoid Arthritis Patients in Clinical Trials with RINVOQ

	Placebo-controlled Studies Week 12/14 (%)			MTX-controlled Studies Week 12/14 (%)		
	Placebo[a] N = 1042	RINVOQ 15 mg[a] N = 1035	Upadacitinib 30 mg[a] N = 384	MTX N = 530	RINVOQ 15 mg N = 534	Upadacitinib 30 mg N = 529
ALT ≥ 3X ULN	1.5	2.1	1.0	1.9	0.8	1.7
AST ≥ 3X ULN	0.7	1.5	0	0.9	0.4	1.3
CPK ≥ 5X ULN[b]	0.3	1.0	0	0	0.8	1.1

ULN = Upper limit of normal in at least one measurement

a. Studies III, IV, V; subjects were permitted background DMARDs.

b. Most elevations > 5X ULN were transient and did not require treatment discontinuation.

Table 16. Hematological changes Reported in Rheumatoid Arthritis Patients in Placebo-controlled Clinical Trials with RINVOQ

	Placebo-controlled Studies		
	Placebo[a] N = 1042 (%)	RINVOQ 15 mg[a] N = 1035 (%)	Upadacitinib 30 mg[a] N = 384 (%)
Neutropenia[b]	< 0.1	1.1	2.4
Lymphopenia[c]	0.7	0.9	2.4
Anemia[d]	< 0.1	< 0.1	0

ULN = Upper limit of normal in at least one measurement

a. subjects were permitted background DMARDs.

b. Decrease in neutrophil counts, below 1 x 10^9 cells/L in at least one measurement. In clinical studies, treatment was interrupted in response to ANC less than 1 x 10^9 cells/L.

c. Decrease in lymphocyte counts, below 0.5 x 10^9 cells/L in at least one measurement.

d. Decrease in hemoglobin, below 80 g/L in at least one measurement.

Lipid Elevations

RINVOQ 15 mg treatment was associated with dose-related increases in total cholesterol, triglycerides, and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled studies, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 0.38 mmol/L and 0.44 mmol/L.
- Mean HDL cholesterol increased by 0.21 mmol/L and 0.23 mmol/L.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 0.15 mmol/L and 0.16 mmol/L.

Psoriatic Arthritis

In the controlled clinical trials in psoriatic arthritis, changes in hematologic and clinical chemistry findings observed with RINVOQ treatment were similar to the changes observed in clinical trials in RA.

Axial Spondyloarthritis

In the controlled clinical trials in ankylosing spondylitis and non-radiographic axial spondyloarthritis, changes in hematologic and clinical chemistry findings observed with RINVOQ treatment were similar to the changes observed in clinical trials in RA and PsA.

Atopic Dermatitis

Clinically significant changes in hematology and chemistry laboratory findings during the clinical trials are presented in **Table 17** and **Table 18**.

Table 17. Biochemical changes Reported in Atopic Dermatitis Patients in Clinical Trials with RINVOQ

	Placebo-controlled Studies Week 16 (%)		
	Placebo N = 902	**RINVOQ 15 mg N = 899**	**RINVOQ 30 mg N = 906**
ALT ≥ 3X ULN	1.1	0.7	1.4
AST ≥ 3X ULN	0.9	1.2	1.1
CPK ≥ 5X ULN[a]	1.7	3.3	4.4

ULN = Upper limit of normal in at least one measurement

a. Most elevations > 5X ULN were transient and did not require treatment discontinuation.

Table 18. Hematological changes Reported in Atopic Dermatitis Patients in Placebo-controlled Clinical Trials with RINVOQ

	Placebo-controlled Studies		
	Placebo N= 902 (%)	**RINVOQ 15 mg N= 899 (%)**	**RINVOQ 30 mg N= 906 (%)**
Neutropenia[a]	0	0.4	1.3
Lymphopenia[b]	0.1	0.1	0.3
Anemia[c]	0	0	0.1

ULN = Upper limit of normal in at least one measurement

a. Decrease in neutrophil counts, below 1 x 10^9 cells/L in at least one measurement. In clinical studies, treatment was interrupted in response to ANC less than 1 x 10^9 cells/L.

b. Decrease in lymphocyte counts, below 0.5 x 10^9 cells/L in at least one measurement.

c. Decrease in hemoglobin, below 80 g/L in at least one measurement.

Lipid Elevations

RINVOQ treatment was associated with dose- related increases in lipid parameters including total cholesterol, LDL cholesterol, and HDL cholesterol.

In controlled studies, for up to 16 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 0.21 mmol/L and 0.34 mmol/L in the RINVOQ 15 mg and 30 mg groups, respectively.
- Mean HDL cholesterol increased by 0.19 mmol/L and 0.24 mmol/L in the RINVOQ 15 mg and 30 mg groups, respectively.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 0.09 mmol/L and 0.09 mmol/L in the RINVOQ 15 mg and 30 mg groups, respectively.

Small increases in LDL cholesterol were observed after Week 16.

Ulcerative Colitis

Clinically significant changes in hematology and chemistry laboratory findings during the clinical trials are presented in **Table 19** and **Table 20**

Table 19. Biochemical changes Reported in Ulcerative Colitis Patients in Placebo-controlled Clinical Trials with RINVOQ

	Induction Week 8 (%)		Maintenance Week 52 (%)		
	Placebo N= 378	**RINVOQ 45 mg N= 719**	**Placebo N= 245**	**RINVOQ 15 mg N= 250**	**RINVOQ 30 mg N= 251**
ALT ≥3X ULN	0	1.5	0.8	2.0	4.0
AST ≥3X ULN	0.3	1.5	0.4	1.6	2.0
CPK ≥5X ULN[a]	0.3	2.2	1.2	4.0	6.4

ULN = Upper limit of normal in at least one measurement

[a] Most elevations > 5 x ULN were transient and did not require treatment discontinuation.

Table 20. Hematological changes Reported in Ulcerative Colitis Patients in Placebo-controlled Clinical Trials with RINVOQ

	Induction Week 8 (%)		Maintenance Week 52 (%)		
	Placebo N= 378	**RINVOQ 45 mg N= 719**	**Placebo N= 245**	**RINVOQ 15 mg N= 250**	**RINVOQ 30 mg N= 251**
Neutropenia[a]	0	2.8	0.8	0.8	2.4
Lymphopenia[b]	0.8	2.0	0.8	1.6	0.8
Anemia[c]	2.1	0.3	1.2	0.4	0.4

[a]Decrease in neutrophil counts, below 1 x 10^9 cells/L in at least one measurement. In clinical studies, treatment was interrupted in response to ANC less than 1 x 10^9 cells/L.
[b]Decrease in lymphocyte counts, below 0.5 x 10^9 cells/L in at least one measurement.
[c]Decrease in hemoglobin, below 80 g/L in at least one measurement.

Lipid elevations

RINVOQ treatment was associated with increases in lipid parameters including total cholesterol, LDL cholesterol, and HDL cholesterol in placebo-controlled induction and maintenance studies over 8 and 52 weeks, respectively. Changes from baseline in lipid parameters are summarized below:

- Mean total cholesterol increased by 0.95 mmol/L in the RINVOQ 45 mg induction group and by 0.87 mmol/L and 1.19 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean HDL increased by 0.44 mmol/L in the RINVOQ 45 mg induction group and by 0.21 mmol/L and 0.34 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean LDL increased by 0.52 mmol/L in the RINVOQ 45 mg induction group and by 0.65 mmol/L and 0.83 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean triglycerides decreased by 0.05 mmol/L in the RINVOQ 45 mg induction group and increased by 0.03 mmol/L and 0.08 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.

Crohn's Disease

Clinically significant changes in hematology and chemistry laboratory findings during the clinical trials are presented in **Table 21** and **Table 22**.

Table 21. Biochemical Changes Reported in Crohn's Disease Patients in Clinical Trials with RINVOQ

	Placebo-Controlled Induction Studies Week 12 (%)		Placebo-Controlled Maintenance and Study Long-term[b] (%)		
	Placebo N = 347	RINVOQ 45 mg N = 674	Placebo N = 223	RINVOQ 15 mg N = 221	RINVOQ 30 mg N = 229
ALT ≥3X ULN	2.9	2.1	1.8	2.3	4.4
AST ≥3X ULN	0.9	1.5	1.4	1.8	2.2
CPK ≥5X ULN[a]	0.6	2.4	0.9	2.3	4.8

ULN = Upper limit of normal in at least one measurement

a. Most elevations > 5 x ULN were transient and did not require treatment discontinuation.
b. Includes placebo-controlled maintenance (52-week) and long-term extension periods for patients remaining on the same dose.

Table 22. Hematological changes Reported in Crohn's Disease Patients in Clinical Trials with RINVOQ

	Placebo-Controlled Induction Studies Week 12 (%)		Placebo-Controlled Maintenance and Long-term Study[d] (%)		
	Placebo N = 347	RINVOQ 45 mg N = 674	Placebo N = 223	RINVOQ 15 mg N = 221	RINVOQ 30 mg N = 229
Neutropenia[a]	0	0.9	0	1.4	2.6
Lymphopenia[b]	2.0	2.2	1.8	4.6	5.2
Anemia[c]	1.4	2.7	2.8	1.4	4.4

ULN = Upper limit of normal in at least one measurement

a. Decrease in neutrophil counts, below 1 x 10^9 cells/L in at least one measurement. In clinical studies, treatment was interrupted in response to ANC less than 1 x 10^9 cells/L.
b. Decrease in lymphocyte counts, below 0.5 x 109 cells/L in at least one measurement.
c. Decrease in hemoglobin, below 80 g/L in at least one measurement.
d. Includes placebo-controlled maintenance (52-week) and long-term extension periods for patients remaining on the same dose.

Lipid Elevations

RINVOQ treatment was associated with dose-related increases in lipid parameters including total cholesterol, LDL cholesterol, and HDL cholesterol in placebo-controlled induction and maintenance

studies over 12 weeks and long-term (including placebo-controlled 52-week maintenance and long-term extension periods for patients remaining on the same dose), respectively. Changes from baseline in lipid parameters are summarized below:

- Mean total cholesterol increased by 0.60 mmol/L in the RINVOQ 45 mg induction group and by 0.50 mmol/L and 0.68 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean HDL cholesterol increased by 0.23 mmol/L in the RINVOQ 45 mg induction group and by 0.14 mmol/L and 0.16 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean LDL cholesterol increased by 0.35 mmol/L in the RINVOQ 45 mg induction group and by 0.37 mmol/L and 0.53 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean triglycerides increased by 0.03 mmol/L in the RINVOQ 45 mg induction group and had no change in the RINVOQ 15 mg and 30 mg maintenance groups.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-market use of RINVOQ. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro assessment of interactions

In vitro metabolism studies indicated that upadacitinib metabolism is mediated by CYP3A4 with a potential minor contribution from CYP2D6.

In vitro studies indicate that upadacitinib does not inhibit or induce the activity of cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) or the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations.

In vitro, upadacitinib is a substrate for the efflux transporters P-gp and BCRP.

9.3 Drug-Behavioural Interactions

Not applicable.

9.4 Drug-Drug Interactions

Potential for Other Drugs to Affect the Pharmacokinetics of Upadacitinib

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole and clarithromycin). RINVOQ 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. RINVOQ 30 mg once daily dose is not

recommended for patients receiving chronic treatment with strong CYP3A4 inhibitors. For patients with ulcerative colitis using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily (for up to 8 weeks) and the recommended maintenance dose is 15 mg once daily (see **4.1 Dosing Considerations**). For patients with Crohn's disease using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily (for up to 12 weeks) and the recommended maintenance dose is 15 mg once daily.

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended (see **4.1 Dosing Considerations**).

The effect of co-administered drugs on upadacitinib plasma exposures is provided in **Table 23**. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 23. Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
Methotrexate	10 to 25 mg/week	6 to 24 mg BID[b]	11	0.97 (0.86-1.09)	0.99 (0.93-1.06)	No dose adjustment of RINVOQ is required
Strong CYP3A4 inhibitor: Ketoconazole	400 mg QD x 6 days	3 mg single dose[b]	11	1.70 (1.55-1.89)	1.75 (1.62-1.88)	RINVOQ 15 mg once daily is the recommended dose for rheumatoid arthritis and psoriatic arthritis and atopic dermatitis. Use RINVOQ with caution if used chronically. For ulcerative colitis and Crohn's Disease, the induction dose should be reduced to 30 mg and the maintenance dose should be reduced to 15 mg when combined with

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
						strong CYP3A4 inhibitors.
Strong CYP3A4 inducer: Rifampin	600 mg QD x 9 days	12 mg single dose[b]	12	0.49 (0.44-0.55)	0.39 (0.37-0.42)	Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended
OATP1B inhibitor: Rifampin	600 mg single dose	12 mg single dose[b]	12	1.14 (1.02- 1.28)	1.07 (1.01-1.14)	No dose adjustment of RINVOQ is required

a. Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs administration of upadacitinib alone. Data represent the point estimates and the corresponding 90% confidence intervals for the difference of the least square means obtained from the repeated measures analyses of the natural logarithms of C_{max} and AUC.

b. Upadacitinib was administered as an immediate-release formulation.

Methotrexate, inhibitors of organic anion transporting polypeptide 1B (OATP1B) transporters, and pH modifying medications (e.g., antacids or proton pump inhibitors) have no effect on upadacitinib plasma exposures (based on in vitro assessments and population pharmacokinetic analyses). CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics (based on population pharmacokinetic analyses), indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures.

Potential for Upadacitinib to Affect the Pharmacokinetics of Other Drugs

The effect of upadacitinib on plasma exposures of other drugs is provided in **Table 24.** The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 24. Drug Interactions: Change in Pharmacokinetics of Co-administered Drugs in the Presence of Upadacitinib

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
Methotrexate	10 to 25 mg/week	6 mg to 24 mg BID x 27 days	11	1.03 (0.86-1.23)	1.14 (0.91-1.43)	No dose adjustment of methotrexate is required
Sensitive CYP1A2 Substrate Caffeine	200 mg single dose	30 mg QD x 10 days	20	1.13 (1.05-1.22)	1.22 (1.15-1.29)	No dose adjustment of CYP1A2 drug substrates is required
	200 mg single dose	45 mg QD x 10 days	18	1.05 (0.97-1.14)	1.04 (0.95-1.13)	
Sensitive CYP3A Substrate Midazolam	5 mg single dose	30 mg QD x 10 days	20	0.74 (0.68-0.80)	0.74 (0.68-0.80)	No dose adjustment of CYP3A drug substrates is required
	5 mg single dose	45 mg QD x 10 days	19	0.75 (0.69-0.83)	0.76 (0.69-0.83)	
Sensitive CYP2D6 Substrate Dextromethorphan	30 mg single dose	30 mg QD x 10 days	20	1.09 (0.98-1.21)	1.07 (0.95-1.22)	No dose adjustment of CYP2D6 drug substrates is required
	30 mg single dose	45 mg QD x 10 days	19	1.30 (1.13-1.50)	1.35 (1.18-1.54)	
Sensitive CYP2C9 Substrate S-Warfarin	10 mg single dose	30 mg QD x 10 days	20	1.07 (1.02-1.11)	1.11 (1.07-1.15)	No dose adjustment of CYP2C9 drug substrates is required
	10 mg single dose	45 mg QD x 10 days	18	1.18 (1.05-1.33)	1.12 (1.05-1.20)	
Sensitive CYP2C19 Marker 5-OH Omeprazole to Omeprazole metabolic ratio	40 mg single dose omeprazole	30 mg QD x 10 days	20	--	1.09 (1.00-1.19)	No dose adjustment of CYP2C19 drug substrates is required
	40 mg single dose omeprazole	45 mg QD x 10 days	18	--	0.96 (0.90-1.02)	
CYP2B6 Substrate Bupropion	150 mg single dose	30 mg QD x 10 days	22	0.87 (0.79-0.96)	0.92 (0.87-0.98)	No dose adjustment of CYP2B6 drug substrates is required

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
Rosuvastatin	5 mg single dose	30 mg QD x 10 days	12	0.77 (0.63-0.94)	0.67 (0.56-0.82)	No dose adjustment of rosuvastatin is required
Atorvastatin	10 mg single dose	30 mg QD x 10 days	24	0.88 (0.79-0.97)	0.77 (0.70-0.85)	No dose adjustment of atorvastatin is required
Ethinylestradiol	0.03 mg single dose	30 mg QD x 11 days	22	0.96 (0.89-1.02)	1.11 (1.04-1.19)	No dose adjustment of ethinylestradiol is required
Levonorgestrel	0.15 mg single dose	30 mg QD x 11 days	22	0.96 (0.87-1.06)	0.96 (0.85-1.07)	No dose adjustment of levonorgestrel is required

a. Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs administration of medication alone. Data represent the point estimates and the corresponding 90% confidence intervals for the difference of the least square means obtained from the repeated measures analyses of the natural logarithms of C_{max} and AUC.

Immunosuppressants, Other JAK Inhibitors, or Biologic DMARDs

There is a risk of added immunosuppression when RINVOQ is co-administered with other potent immunosuppressive drugs (e.g., tacrolimus, cyclosporine, azathioprine). The combined use of RINVOQ with other potent immunosuppressants, other JAK inhibitors, or biologic DMARDs has not been evaluated in clinical studies and is not recommended (see **4.1 Dosing Considerations** and **7 WARNINGS AND PRECAUTIONS**).

9.5 Drug-Food Interactions

Grapefruit inhibits CYP3A-mediated metabolism. RINVOQ should be used with caution when administered concomitantly with grapefruit juice.

Following single dose oral administration of RINVOQ extended-release tablets with a high-fat, high-calorie meal, there was an increase in upadacitinib AUC_T and C_{max} when compared to administration under fasting conditions (see **10.3 Pharmacokinetics**); however, RINVOQ can be administered with or without food (see **4.4 Administration** and **14 CLINICAL TRIALS**).

9.6 Drug-Herb Interactions

St John's Wort is a CYP3A inducer which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with St John's Wort is not recommended.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Upadacitinib is a Janus Kinase (JAK) inhibitor. JAKs are intracellular enzymes that transduce signals from cell surface receptors for cytokines or growth factors involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2).

Upadacitinib inhibits JAKs with a high degree of selectivity against other kinases in the human genome. In cell-free isolated enzyme assays, upadacitinib had greater inhibitory potency at JAK1 relative to JAK2, JAK3 and TYK2 with IC50 values of 43, 120, 2300, and 4700 nM for JAK1, JAK2, JAK3, and TYK2, respectively. However, in human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation. Upadacitinib blocked IL-2 induced (JAK1/JAK3) and IL-6 induced (JAK1/JAK2) STAT phosphorylation at 9 to 13 nM and erythropoietin induced (JAK2/JAK2) STAT phosphorylation at 628 nM.

Pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) transduce signals via the JAK1 pathway and are involved in atopic dermatitis pathogenesis. JAK1 inhibition with upadacitinib modulates the signaling of the JAK-dependent cytokines underlying the signs and symptoms of atopic dermatitis, including chronic eczematous rash and pruritus, and underlying the inflammatory burden and signs and symptoms of ulcerative colitis. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15, and IFNγ) transduce signals via the JAK1 pathway and are involved in pathology of inflammatory bowel diseases. JAK1 inhibition with upadacitinib modulates the signaling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of inflammatory bowel diseases. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

10.2 Pharmacodynamics

Inhibition of IL-6 Induced STAT3 and IL-7 Induced STAT5 Phosphorylation

In healthy volunteers, the administration of upadacitinib (immediate release formulation) resulted in a dose- and concentration-dependent inhibition of IL-6 (JAK1/JAK2)-induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.

Lymphocytes

In patients with rheumatoid arthritis, treatment with upadacitinib was associated with a small, transient increase in mean ALC from baseline up to Week 36 which gradually returned to, at or near baseline levels with continued treatment.

Immunoglobulins

In patients with rheumatoid arthritis, small decreases from baseline in mean IgG and IgM levels were observed with upadacitinib treatment in the controlled period of the clinical studies; however, the mean values at baseline and at all visits were within the normal reference range.

High-sensitivity C-reactive Protein (hsCRP) and Other Markers of Inflammation

In patients with rheumatoid arthritis, treatment with upadacitinib was associated with significant decreases from baseline in mean hsCRP levels as early as Week 1, which were maintained with continued treatment.

In patients with ulcerative colitis, treatment with upadacitinib was associated with decreases from baseline in mean hsCRP levels as early as Week 2 which were maintained with continued treatment through Week 52.

In patients with Crohn's disease, reductions in hsCRP and fecal calprotectin (FCP) were observed after treatment with upadacitinib. Decreases in hsCRP and FCP were maintained out to Week 52 in the maintenance study.

Fecal Calprotectin

In patients with ulcerative colitis, treatment with upadacitinib 45 mg was associated with improvement from baseline fecal calprotectin, which was then maintained with upadacitinib 15 mg and 30 mg treatment through Week 52.

Cardiac Electrophysiology

The effect of upadacitinib on QTc interval was evaluated in subjects who received single and multiple doses of upadacitinib. Upadacitinib does not prolong QTc interval at therapeutic or supratherapeutic plasma concentrations.

Vaccine Study

Humoral response following the administration of pneumococcal 13-valent conjugate vaccine was evaluated in 111 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg (n = 87) or 30 mg (n = 24). The majority of patients were female (85.6%) and 97% of patients (n = 108) were on concomitant methotrexate. A ≥ 2-fold increase in antibody concentration to ≥ 6 of 12 pneumococcal antigens was achieved by 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with upadacitinib 15 mg and 30 mg, respectively.

10.3 Pharmacokinetics

Absorption: Upadacitinib is absorbed following administration of the extended-release formulation with a median time to maximum observed plasma concentration (T_{max}) of approximately 2 to 3 hours under fasting conditions and 4 hours under non-fasting conditions. Upadacitinib plasma exposures are proportional to dose over the range of 7.5 mg to 45 mg using the extended-release formulation under fasting conditions.

Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once-daily administrations using the 15 mg extended-release formulation. The pharmacokinetics of upadacitinib do not change over time.

The pharmacokinetic properties of RINVOQ are provided in **Table 25**.

Table 25. Summary of RINVOQ's Pharmacokinetic Parameters in Humans

	$C_{max, ss}$ (ng/mL)	$t_{½}$ (h)	$AUC_{τ, ss}$ (ng*hr/mL)	Apparent Oral Clearance (L/h)
Healthy Volunteers	28.1 ± 9.29[a]	8.8 ± 5.4[c]	251 ± 69.8[a]	64.9 ± 18.77[a]
Rheumatoid Arthritis Patients	41.3 ± 7.2[b]	9-14[d]	396 ± 141[b]	40.5 (37)[e]

Abbreviations: $C_{max, ss}$ = maximum observed drug concentration; $t_{1/2}$ = terminal elimination half-life; $AUC_{τ, ss}$ = area under the concentration-time curve during one dosing interval at steady state. Values presented are mean ± standard deviation unless otherwise specified.

a. Summary of pharmacokinetic parameters across Phase 1 studies for 15 mg QD regimen (fasting and non-fasting conditions).
b. Summary of upadacitinib model-estimated exposures in RA patients in Phase 3 studies.
c. Harmonic mean ± pseudo-standard deviation across Phase 1 studies for 15 mg QD regimen (fasting and non-fasting conditions).
d. Harmonic mean range for the extended-release formulation in healthy subjects in Study M14-680.
e. Apparent oral clearance in RA patients from population pharmacokinetic analysis represented as parameter estimate (percent inter-subject variability).

Following single dose oral administration of RINVOQ extended-release tablets with a high-fat, high-calorie meal, there was an increase in upadacitinib AUC_T and C_{max} of approximately 27% and 63%, respectively for the 15 mg strength, 21% and 36%, respectively for the 30 mg strength, and 27% and 60%, respectively for the 45 mg strength when compared to administration under fasting conditions. In clinical trials, upadacitinib was administered without regard to meals (see **4.2 Recommended Dose and Dosage Adjustment**).

Distribution: Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components with a blood to plasma ratio of 1.0.

Metabolism: Upadacitinib metabolism is mediated by mainly CYP3A4 with a potential minor contribution from CYP2D6. The pharmacologic activity of upadacitinib is attributed to the parent molecule. In a human radiolabeled study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma while the main metabolite detected (product of monooxidation followed by glucuronidation) accounted for 13% of the total plasma radioactivity. No active metabolites have been identified for upadacitinib.

Elimination: Following single dose administration of (^{14}C)upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent substance in urine (24%) and feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours. Subjects with rheumatoid arthritis (RA) are estimated to have ~38% lower upadacitinib CL/F compared to healthy subjects (**Table 25**).

Special Populations and Conditions

- **Pediatrics**

  No meaningful difference in the systemic exposure of upadacitinib was observed in pediatric patients with atopic dermatitis 12 years of age and older weighing at least 40 kg compared to adults.

- **Geriatrics**

  Age did not have a clinically meaningful effect on upadacitinib exposure. (see **4.2 Recommended Dose and Dosage Adjustment**).

- **Other Intrinsic Factors**

  Age, sex, body weight, race and ethnicity did not have a clinically meaningful effect on upadacitinib exposure. Upadacitinib pharmacokinetic exposures are generally consistent across rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, ulcerative colitis and Crohn's Disease patients.

- **Hepatic Impairment**

  Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC_{inf} was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib C_{max} was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C) and should not be intitated in this patient population (see **4.2 Recommended Dose and Dosage Adjustment**).

- **Renal Impairment**

  Upadacitinib AUC_{inf} was 18, 33, and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function. For dosing in patients with renal impairment see **4.2 4.2 Recommended Dose and Dosage** Adjustment.

11 STORAGE, STABILITY AND DISPOSAL

Temperature:

Store at 2 to 25°C.

Moisture:

Store in the original bottle, containing a 3 gram desiccant canister, in order to protect from moisture.

Others:

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Upadacitinib (INN)

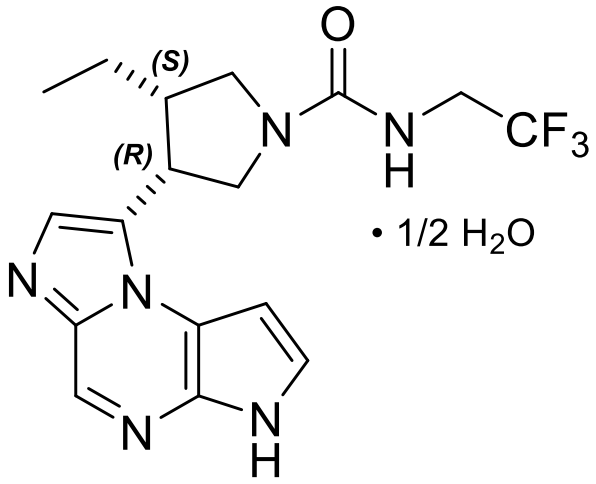
Chemical name: (3S,4R)-3-Ethyl-4-(3H-imidazo(1,2-a)pyrrolo(2,3-e)pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1)

Molecular formula and molecular mass: $C_{17}H_{19}F_3N_6O \bullet ½\ H_2O$ (hemihydrate)

389.38 g/mol (hemihydrate)

380.38 g/mol (anhydrate)

Structural formula:



Physicochemical properties: Upadacitinib is a white to light brown powder. The solubility of upadacitinib in water is 38 to less than 0.2 mg/mL across a pH range of 2 to 9 at 37°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Rheumatoid Arthritis

The efficacy and safety of RINVOQ (upadacitinib) 15 mg once daily were assessed in five Phase 3 randomized, double-blind, multicenter studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria (see **Table 26**). Patients over 18 years of age were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of high-sensitivity C-reactive protein (hsCRP) was required at baseline. Although other doses have been studied, the recommended dose of RINVOQ is 15 mg once daily.

Baseline demographics were generally similar among the treatment groups in each study and comparable between the studies. Typical of the overall rheumatoid arthritis population, the majority of patients were female and white. The mean (standard deviation (SD)) age ranged from 53.4 (12.73) to 57.1 (11.42) years. The baseline demographics in each study are shown in **Table 26.**

Table 26. Summary of patient demographics for clinical trials in Rheumatoid Arthritis

Study #	Study design	Dosage, route of administration and duration	Study subjects, N	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)[f]
STUDY I SELECT-EARLY (M13-545)	Randomized, double-blind, active-controlled, multicenter, in MTX-naïve[a] patients Monotherapy	RINVOQ 15 mg Upadacitinib 30 mg MTX Tablets, orally, once daily Main treatment period: 24 weeks	947	53.4 (12.73)	76.3	2.7 (5.38)
STUDY II SELECT-MONOTHERAPY (M15-555)	Randomized, double-blind, active-controlled, multicenter, in MTX-IR[b] patients Monotherapy	RINVOQ 15 mg Upadacitinib 30 mg MTX Tablets, orally, once daily Main treatment period: 14 weeks	648	54.3 (12.05)	80.7	6.6 (7.58)

Study #	Study design	Dosage, route of administration and duration	Study subjects, N	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)[f]
STUDY III SELECT-NEXT (M13-549)	Randomized, double-blind, placebo-controlled, multicenter, in csDMARD-IR[c] patients On background csDMARDs	RINVOQ 15 mg Upadacitinib 30 mg Placebo Tablets, orally, once daily Main treatment period: 12 weeks	661	55.7 (11.65)	78.7	7.3 (7.72)
STUDY IV SELECT-COMPARE (M14-465)	Randomized, double-blind, placebo- and active-controlled, multicenter, in MTX-IR[d] patients On background MTX	RINVOQ 15 mg Placebo Tablets, orally, once daily Adalimumab 40 mg EOW Main treatment period: 26 weeks	1629	53.9 (12.07)	79.3	8.2 (7.97)
STUDY V SELECT-BEYOND (M13-542)	Randomized, double-blind, placebo-controlled, multicenter, in bDMARD-IR[e] patients On background csDMARDs	RINVOQ 15 mg Upadacitinib 30 mg Placebo Tablets, orally, once daily Main treatment period: 12 weeks	499	57.1 (11.42)	83.9	13.2 (9.45)

a. Patients were naïve to MTX or received no more than 3 weekly MTX doses

b. Patients had inadequate response to MTX

c. Patients who had an inadequate response to csDMARDs; patients with prior exposure to at most one bDMARD were eligible (up to 20% of total number of patients) if they had either limited exposure (< 3 months) or had to discontinue the bDMARD due to intolerability

d. Patients who had an inadequate response to MTX; patients with prior exposure to at most one bDMARD (except adalimumab) were eligible (up to 20% of total study number of patients) if they had either limited exposure (< 3 months) or had to discontinue the bDMARD due to intolerability

e. Patients who had an inadequate response or intolerance to at least one bDMARD

f. Years since RA diagnosis

Study I (M13-545) was a 48-week trial in 947 patients with moderately to severely active rheumatoid arthritis who were naïve to methotrexate (MTX). Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or MTX as monotherapy. At Week 26, non-responding patients on upadacitinib could be rescued with the addition of MTX, while patients on MTX could be rescued with the addition of blinded RINVOQ 15 mg or upadacitinib 30 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR50 response at Week 12. Key secondary endpoints included disease activity score (DAS28-CRP) ≤ 3.2 at Week 12, DAS28-CRP < 2.6 at Week 24, change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 12, and change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Week 24.

Study II (M15-555) was a 14-week monotherapy trial in 648 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily monotherapy or continued their stable dose of MTX monotherapy. At Week 14, patients who were randomized to MTX were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily monotherapy in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 14. Key secondary endpoints included DAS28-CRP ≤ 3.2, DAS28-CRP < 2.6, and change from baseline in HAQ-DI at Week 14.

Study III (M13-549) was a 12-week trial in 661 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background csDMARD therapy. At Week 12, patients who were randomized to placebo were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. Key secondary endpoints included DAS28-CRP ≤ 3.2, DAS28-CRP < 2.6, and change from baseline in HAQ-DI at Week 12.

Study IV (M14-465) was a 48-week trial in 1629 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received RINVOQ 15 mg once daily, adalimumab, or placebo added to background MTX. From Week 14, non-responding patients on RINVOQ 15 mg could be rescued to adalimumab in a blinded manner, and non-responding patients on adalimumab or placebo could be rescued to RINVOQ 15 mg in a blinded manner. At Week 26, all patients randomized to placebo were switched to RINVOQ 15 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12 versus placebo. Key secondary endpoints versus placebo included DAS28-CRP ≤ 3.2, DAS28-CRP < 2.6, change from baseline in HAQ-DI at Week 12, and change from baseline in mTSS at Week 26.

Study V (M13-542) was a 12-week trial in 499 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to biologic DMARDs. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background csDMARD therapy. At Week 12, patients who were randomized to placebo were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. Key secondary endpoints included DAS28-CRP ≤ 3.2 and change from baseline in HAQ-DI at Week 12.

Study Results

The percentages of patients treated with RINVOQ 15 mg achieving ACR20, ACR50, and ACR70 responses, DAS28-CRP < 2.6 in all studies are shown in **Table 27**.

In all studies, patients treated with RINVOQ 15 mg, alone or in combination with csDMARDs, achieved significantly higher ACR20, ACR50, and ACR70 response rates compared to MTX monotherapy or placebo, respectively, at the primary efficacy time point, except for ACR70 in Study V (**Table 27**).

In Study IV, the percentage of patients achieving ACR20 responses by visit is shown in **Figure 1**. In Studies III and V, significantly higher ACR20 response rates were observed as early as Week 1 with RINVOQ 15 mg versus placebo.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in significantly greater improvements in the individual ACR components compared to placebo or MTX at the primary efficacy time point (**Table 28**).

Table 27. Proportion of Patients Achieving ACR Responses and DAS28-CRP < 2.6

Efficacy Measure	Study	Study I MTX-Naïve		Study II MTX-IR		Study III csDMARD-IR		Study IV[h] MTX-IR			Study V bDMARD-IR	
		Monotherapy		Monotherapy		Background csDMARDs		Background MTX			Background csDMARDs	
		MTX	RINVOQ 15 mg % Δ (95% CI)	MTX	RINVOQ 15 mg % Δ (95% CI)	PBO	RINVOQ 15 mg % Δ (95% CI)	PBO	RINVOQ 15 mg % Δ (95% CI)	ADA 40 mg	PBO	RINVOQ 15 mg % Δ (95% CI)
	Week	N = 314	317	216	217	221	221	651	651	327	169	164
ACR 20[f]	12[a]/14[b]	54	76[e] 22 (14, 29)	41	68[e] 27 (18, 36)	36	64[e] 28 (19, 37)	36	71[e] 34 (29, 39)	63	28	65[e] 36 (26, 46)
	24[c]/26[d]	59	79[e] 20 (13, 27)					36	67[e] 32 (27, 37)	57		
ACR 50[f]	12[a]/14[b]	28	52[e] 24 (16, 31)	15	42[e] 27 (19, 35)	15	38[e] 23 (15, 31)	15	45[e] 30 (26, 35)	29	12	34[e] 22 (14, 31)
	24[c]/26[d]	33	60[e] 27 (19, 34)					21	54[e] 33 (28, 38)	42		
ACR 70[g]	12[a]/14[b]	14	33[e] 19 (12, 25)	3	23[e] 20 (14, 26)	6	21[e] 15 (9, 21)	5	25[e] 20 (6, 24)	14	7	12 5 (-1, 11)
	24[c]/26[d]	19	45[e] 26 (19, 33)					10	35[e] 25 (21, 29)	23		
DAS28-CRP < 2.6[f]	12[a]/14[b]	14	36[e] 22 (16, 29)	8	28[e] 20 (13, 27)	10	31[e] 21 (14, 28)	6	29[e] 23 (19, 27)	18	10	29[e] 19 (11, 27)
	24[c]/26[d]	19	48[e] 30 (23, 37)					9	41[e] 32 (27, 36)	27		

Patients who discontinued randomized treatment, or had cross-over between randomized treatments, or were missing data at week of evaluation were imputed as non-responders in the analyses.

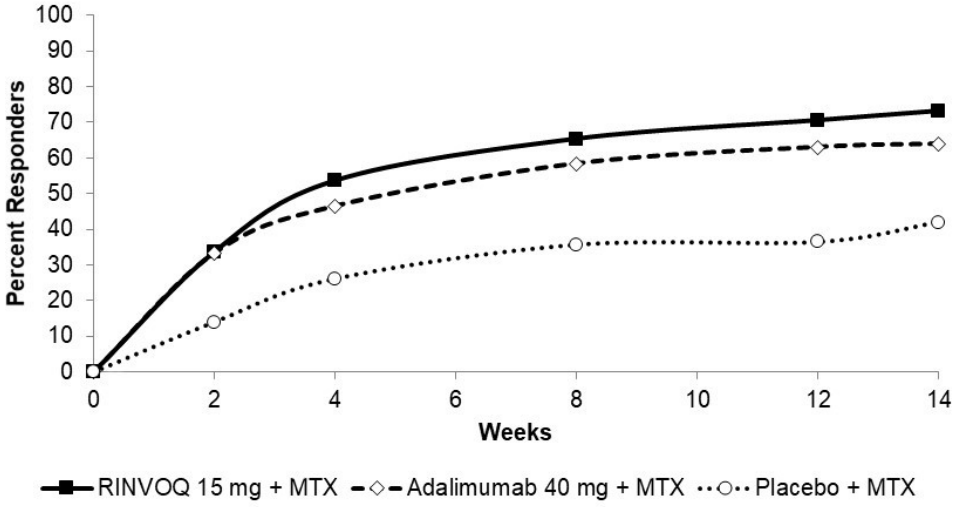
a. Study I, Study III, Study IV, Study V
b. Study II
c. Study I
d. Study IV
e. $p \leq 0.001$ RINVOQ 15 mg vs placebo or MTX comparison
f. The following comparisons for RINVOQ 15 mg vs placebo or MTX are included in multiplicity adjustment for overall type I error control: ACR20 at Week 12/14 in Study II, Study III, Study IV, and Study V; ACR50 at Week 12 in Study I; DAS28-CRP < 2.6 at Week 24 in Study I, and at Week 12/14 for Study II, Study III, and Study IV.
g. Not included in multiplicity adjustment for overall type I error control.
h. No conclusions can be drawn regarding the superiority of RINVOQ + MTX versus adalimumab + MTX.

Table 28. Components of ACR Response (mean change from baseline)[a]

ACR Component	Study	Study I MTX-Naïve		Study II MTX-IR		Study III csDMARD-IR		Study IV MTX-IR			Study V bDMARD-IR	
		Monotherapy		Monotherapy		Background csDMARDs		Background MTX			Background csDMARDs	
		MTX	RINVOQ 15 mg	MTX	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
	Week	N = 314	317	216	217	221	221	651	651	327	169	164
Number of tender joints (0-68)	12[b]/14[c]	-13	-17[h]	-11	-15[h]	-8	-14[h]	-10	-16[h]	-14	-8	-16[h]
	24[d]/26[e]	-16	-19[h]					-9	-18[h]	-15		
Number of swollen joints (0-66)	12[b]/14[c]	-10	-12[h]	-8	-11[h]	-6	-9[h]	-7	-11[h]	-10	-6	-11[h]
	24[d]/26[e]	-12	-14[h]					-6	-12[h]	-11		
Pain[f]	12[b]/14[c]	-25	-36[h]	-14	-26[h]	-10	-30[h]	-15	-32[h]	-25	-10	-26[h]
	24[d]/26[e]	-28	-40[h]					-19	-37[h]	-32		
Patient global assessment[f]	12[b]/14[c]	-25	-35[h]	-11	-23[h]	-10	-30[h]	-15	-30[h]	-24	-10	-26[h]
	24[d]/26[e]	-28	-39[h]					-18	-36[h]	-30		
Disability Index (HAQ-DI)[g]	12[b]/14[c]	-0.5	-0.8[h]	-0.3	-0.7[h]	-0.3	-0.6[h]	-0.3	-0.6[h]	-0.5	-0.2	-0.4[h]
	24[d]/26[e]	-0.6	-0.9[h]					-0.3	-0.7[h]	-0.6		
Physician global assessment[f]	12[b]/14[c]	-35	-46[h]	-26	-40[h]	-23	-38[h]	-25	-39[h]	-36	-26	-39[h]
	24[d]/26[e]	-45	-50[h]					-27	-45[h]	-41		
hsCRP (mg/L)	12[b]/14[c]	-10.6	-17.5[h]	-1.1	-10.2[h]	-0.4	-10.1[h]	-1.7	-12.5[h]	-9.2	-1.1	-11.0[h]
	24[d]/26[e]	-11.6	-18.4[h]					-1.5	-13.5[h]	-10.3		

a. Data shown are least square (LS) means of change from baseline
b. Study I, Study III, Study IV, Study V
c. Study II, primary efficacy time point is at Week 14
d. Study I
e. Study IV
f. Visual analog scale: 0 = best, 100 = worst
g. Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Data shown are the within group LS means of change from baseline.
h. $p \leq 0.001$ RINVOQ 15 mg vs placebo or MTX comparison

Figure 1. Percent of Patients Achieving ACR20 in Study IV



Patients who discontinued randomized treatment, or were missing ACR20 results, or were lost-to-follow-up or withdrawn from the study were imputed as non-responders.

In Study I and Study IV, a higher proportion of patients treated with RINVOQ 15 mg alone or in combination with MTX, achieved DAS28-CRP < 2.6 compared to MTX or placebo at the primary efficacy time point **(Table 29**).

Table 29. Proportion of Patients with DAS28-CRP Less Than 2.6 with Number of Residual Active Joints at Primary Efficacy Time Point

	Study I MTX-Naïve		**Study IV MTX-IR**	
	Monotherapy		**Background MTX**	
DAS28-CRP Less Than 2.6	**MTX** N = 314	**RINVOQ 15 mg** N = 317	**MTX** N = 651	**RINVOQ 15 mg** N = 651
Proportion of responders at Week 12 (n)	14% (43)	36% (113)	6% (40)	29% (187)
Of responders, proportion with 0 active joints (n)	51% (22)	45% (51)	60% (24)	48% (89)
Of responders, proportion with 1 active joint (n)	35% (15)	23% (26)	20% (8)	23% (43)
Of responders, proportion with 2 active joints (n)	9% (4)	17% (19)	15% (6)	13% (25)
Of responders, proportion with 3 or more active joints (n)	5% (2)	15% (17)	5% (2)	16% (30)

Radiographic Response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score, and joint space narrowing score at Week 26 in Study IV and Week 24 in Study I. The proportion of patients with no radiographic progression (mTSS change from baseline ≤ 0) was also assessed.

In Study IV, treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Weeks 26 (**Table 30**). Analyses of erosion and joint space narrowing scores were consistent with overall results. In this study, 76% of patients in the

placebo plus MTX group experienced no radiographic progression at Week 26 compared to 84% of patients treated with RINVOQ 15 mg.

In Study I, treatment with RINVOQ 15 mg monotherapy resulted in significantly greater inhibition of the progression of structural joint damage compared to MTX monotherapy at Week 24 (**Table 30**). Analyses of erosion and joint space narrowing scores were consistent with overall results. In this study, 78% of the patients in the MTX monotherapy group experienced no radiographic progression at Week 24 compared to 88% of the patients treated with RINVOQ 15 mg monotherapy.

Table 30. Radiographic Changes

Measurement tool	**Study**	**Study I MTX-Naïve**		**Study IV MTX-IR**		
		Monotherapy		**Background MTX**		
	Treatment Group	**MTX**	**RINVOQ 15 mg Δ (95% CI)**	**PBO[a]**	**RINVOQ 15 mg Δ (95% CI)**	**ADA 40 mg**
	Week					
Modified Total Sharp Score, mean change from baseline	24[b]/26[c]	0.7	0.1[f] -0.5 (-0.9, -0.2)	0.9	0.2[e] -0.7 (-1.0, -0.4)	0.1
Erosion Score, mean change from baseline	24[b]/26[c]	0.3	0.1[e] -0.3 (-0.4, -0.1)	0.4	0[e] -0.4 (-0.6, -0.2)	0
Joint Space Narrowing Score, mean change from baseline	24[b]/26[c]	0.3	0.1[g] -0.2 (-0.4, -0.0)	0.6	0.2[e] -0.4 (-0.6, -0.2)	0.1
Proportion of patients with no radiographic progression[d]	24[b]/26[c]	77.7	87.5[f] 9.8 (3.5, 16.2)	76.0	83.5[f] 7.5 (3, 12.1)	86.8

a. Analyses are based on linear extrapolation
b. Study I
c. Study IV
d. No progression defined as mTSS change ≤ 0
e. p ≤ 0.001 RINVOQ 15 mg vs placebo or MTX comparison
f. p ≤ 0.01 RINVOQ 15 mg vs placebo or MTX comparison
g. p ≤ 0.05 RINVOQ 15 mg vs placebo or MTX comparison

Physical Function Response and Health-Related Outcomes

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in a significant improvement in physical function compared to all comparators (placebo, MTX, or adalimumab) as measured by HAQ-DI at Week 12/14 (**Table 31**).

In Studies II, III, and IV, treatment with RINVOQ 15 mg resulted in a significantly greater improvement in the mean duration of morning joint stiffness compared to placebo or MTX at Week 12/14.

Other Health-Related Outcomes

Across all studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in physical component summary (PCS) score, mental component summary (MCS) scores, and in all 8 domains of the Short Form Health Survey (SF-36) compared to placebo in combination with csDMARDs or MTX monotherapy at Week 12/14.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in Studies I, III, and IV. Improvement in fatigue at Week 12 was observed in patients treated with RINVOQ 15 mg compared to patients on placebo in combination with csDMARDs MTX monotherapy.

Table 31. Physical Function Response HAQ-DI (MCID) at Week 12[b]/14[c]

Study	Study I MTX-Naïve		Study II MTX-IR		Study III csDMARD-IR		Study IV MTX-IR			Study V bDMARD-IR	
	MTX	RINVOQ 15 mg	MTX	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
N	**314**	**317**	**216**	**217**	**221**	**221**	**651**	**651**	**327**	**169**	**164**
Change from Baseline[a] Δ (95% CI)	-0.49	-0.83[d] -0.34 (-0.44, -0.25)	-0.32	-0.65[d] -0.33 (-0.43, -0.22)	-0.25	-0.59[d] -0.33 (-0.43, -0.24)	-0.28	-0.60[d] -0.31 (-0.37, -0.25)	-0.49	-0.17	-0.39[d] -0.22 (-0.34, -0.10)
HAQ-DI Responder Rates[e] (%)	54	77[d]	39	62[d]	43	67[d]	44	64[d]	64	27	56[d]

a. Data shown are least squares (LS) mean
b. Studies I, III, IV and V
c. Study II
d. $p \leq 0.001$ RINVOQ 15 mg vs placebo or MTX comparison
e. Percentage of patients with an improvement from baseline ≥ 0.30

Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in two Phase 3 randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis (**Table 32**). All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. For both studies, the primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. The studies include long-term extensions for up to 5 years (SELECT-PsA 1) and 3 years (SELECT-PsA 2).

Table 32. Summary of Patient Demographics for Clinical Trials in Psoriatic Arthritis

Study #	Trial design	Dosage, route of administration and duration	Study subjects, N[c]	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)[d]
Study-PsA I SELECT-PsA 1 (M15-572)	Randomized, double-blind, placebo- and active-controlled, multicenter, in non-biologic DMARD-IR[a] patients	RINVOQ 15 mg Upadacitinib 30 mg Placebo, orally, once daily Adalimumab 40 mg EOW Main treatment period: 24 weeks	1704	50.8 (12.22)	53.2	6.1 (6.97)
Study-PsA II SELECT-PsA 2 (M15-554)	Randomized, double-blind, placebo-controlled, multicenter, in bDMARD-IR[b] patients	RINVOQ 15 mg Upadacitinib 30 mg Placebo, orally, once daily Main treatment period: 24 weeks	641	53.4 (11.83)	54.3	10.1 (9.18)

a. Patients who had an inadequate response or intolerance to at least one non-biologic DMARD
b. Patients who had an inadequate response or intolerance to at least one bDMARD
c. Includes all randomized patients who received at least one dose of study drug
d. Years since psoriatic arthritis diagnosis

Study-PsA I (M15-572) was a 24-week trial in 1705 patients who had an inadequate response or intolerance to at least one non-biologic DMARD. At baseline, 1393 (82%) of patients were on at least one concomitant non-biologic DMARD, 1084 (64%) of patients received concomitant MTX only, and 311 (18%) of patients were on monotherapy. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily, adalimumab 40 mg EOW, or placebo. From Week 16, non-responding patients could be rescued with addition or modification of standard of care. At Week 24, all patients randomized to

placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline.

Study-PsA II (M15-554) was a 24-week trial in 642 patients who had an inadequate response or intolerance to at least one biologic DMARD. At baseline, 296 (46%) of patients were on at least one concomitant non-biologic DMARD, 222 (35%) of patients received concomitant MTX only, and 345 (54%) of patients were on monotherapy. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo. From Week 16, non-responding patients could be rescued with addition or modification of standard of care. At Week 24, all patients randomized to placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline.

Study Results

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved ACR20 response compared to placebo at Week 12 (**Table 33**, **Figure 2** for PsA-I). Onset of efficacy was seen as early as Week 2 for ACR20.

Treatment with RINVOQ 15 mg resulted in improvements in individual ACR components, including tender/painful and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP compared to placebo at Week 12 (**Table 34**).

In Study-PsA I, RINVOQ 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at Week 12 with values of 71% and 65% for RINVOQ and adalimumab, respectively; superiority to adalimumab could not be demonstrated.

A higher proportion of patients treated with RINVOQ 15 mg achieved ACR50 and ACR70 responses at Week 12 compared to placebo.

The efficacy of RINVOQ 15 mg, as assessed by ACR20, was demonstrated regardless of subgroups evaluated including baseline BMI, baseline hsCRP, and number of prior non-biologic DMARDs (≤ 1 or > 1).

Within each study, consistent responses were observed with RINVOQ 15 mg alone or in combination with non-biologic DMARDs for primary and key secondary endpoints.

Figure 2. Percent of Patients Achieving ACR20 in Study-PsA I

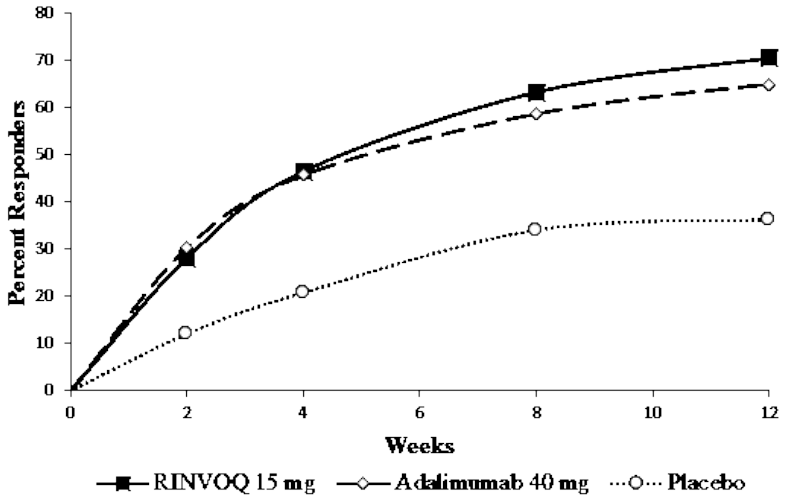


Table 33. Clinical Trial Summary

Efficacy Measure	Study	Study-PsA I non-biologic DMARD-IR			Study-PsA II bDMARD-IR	
	Treatment Group	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
	N	423	429	429	212	211
ACR20 (% of patients)	Week 12	36	71[e]	65	24	57[e]
	Week 24	45	73[f]	67	20	59[f]
ACR50 (% of patients)	Week 12	13	38[f]	38	5	32[f]
	Week 24	19	52[f]	44	9	38[f]
ACR70 (% of patients)	Week 12	2	16[f]	14	1	9[f]
	Week 24	5	29[f]	23	1	19[f]
MDA (% of patients)	Week 24	12	37[e]	33	3	25[e]
Resolution of enthesitis (LEI=0; % of patients)[a]	Week 24	32	54[e]	47		
Resolution of dactylitis (LDI=0; % of patients)[b]	Week 24	40	77[b]	74		
PASI75 (% of patients)[c]	Week 16	21	63[e]	53	16	52[e]
	Week 24	27	64[f]	59	19	54[f]
sIGA 0/1 (% of patients)[d]	Week 16	11	42[e]	39	9	37[e]
Modified Sharp/van der Heijde Score	Baseline	13.05	13.44	14.89		
	Week 24	13.31	13.42[e]	14.92		

Patients who discontinued randomized treatment or were missing data at week of evaluation were imputed as non-responders in the analyses. For MDA, resolution of enthesitis, and resolution of dactylitis at Week 24, the subjects rescued at Week 16 were imputed as non-responders in the analyses.

a. In patients with enthesitis at baseline (n = 241, 270, and 265, respectively)
b. In patients with dactylitis at baseline (n = 126, 136, and 127, respectively). Statistical significance cannot be claimed for this endpoint based on step-down testing procedure.
c. In patients with ≥ 3% BSA psoriasis at baseline (n = 211, 214, and 211, respectively, for Study-PsA I and n = 131 and 130, respectively, for Study-PsA II)
d. In patients with sIGA ≥ 2 at baseline (n = 313, 322, and 330, respectively, for Study-PsA I and n = 163 and 171, respectively, for Study-PsA II)
e. multiplicity-controlled p ≤ 0.001 RINVOQ vs placebo comparison. For modified Sharp/van der Heijde score, the comparison is based on analysis of covariance model for change from baseline with missing data handled by linear extrapolation.
f. nominal p ≤ 0.001 RINVOQ vs placebo comparison

Radiographic Response

In Study-PsA I, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Sharp/van der Heijde Score (SHS). Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage as measure by SHS compared to placebo at Week 24 (**Table 34**). Similar results were observed for both of the SHS components, joint erosion, and joint space narrowing scores.

Table 34. Components of ACR Response

ACR Component	Study	Study-PsA I non-biologic DMARD-IR			Study-PsA II bDMARD-IR	
	Treatment Group	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
	N	423	429	429	212	211
Number of tender/painful joints (0-68)	Baseline	19.6	20.4	19.9	25.4	24.8
	Week 12	12.4	8.7[d]	9.3	19.3	12.2[d]
Number of swollen joints (0-66)	Baseline	10.9	11.5	11.6	11.8	11.2
	Week 12	5.6	3.4[d]	3.7	7.2	4.4[d]
Patient assessment of pain[a]	Baseline	6.1	6.2	5.9	6.6	6.3
	Week 12	5.1	3.8[d]	3.6	6.0	4.4[d]
Patient global assessment[a]	Baseline	6.3	6.6	6.3	6.9	6.8
	Week 12	5.2	3.8[d]	3.7	6.1	4.5[d]
Disability index (HAQ-DI)[b]	Baseline	1.11	1.15	1.11	1.23	1.08
	Week 12	0.98	0.72[c]	0.78	1.12	0.79[c]
Physician global assessment[a]	Baseline	6.5	6.7	6.6	6.4	6.5
	Week 12	4.3	3.0[d]	3.1	5.0	3.3[d]
hsCRP (mg/L)	Baseline	11.3	11.3	11.0	9.0	11.2
	Week 12	10.2	4.2[d]	3.7	9.6	3.9[d]

a. Numeric rating scale (NRS): 0 = best, 10 = worst
b. Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
c. multiplicity-controlled $p \leq 0.001$ is based on mixed model for repeated measures for change from baseline for RINVOQ vs placebo comparison
d. nominal $p \leq 0.001$ is based on mixed model for repeated measures for change from baseline for RINVOQ vs placebo comparison

Response rates for ACR20/50/70, MDA, PASI75, sIGA, enthesitis resolution, and dactylitis resolution in patients treated with RINVOQ 15 mg were maintained through Week 56.

Physical Function Response and Health-Related Outcomes

In both studies, patients treated with RINVOQ 15 mg showed significant improvement from baseline in physical function as assessed by HAQ-DI at Week 12 when compared to placebo (**Table 34**), which was maintained through Week 56.

Health-related quality of life was assessed by SF-36. In both studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared to placebo at Week 12. Improvements from baseline were maintained through Week 56 in both studies.

Patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score, at Week 12 compared to placebo in both studies. Improvements from baseline were maintained through Week 56 in both studies.

Axial Spondyloarthritis

Ankylosing Spondylitis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in two randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with active ankylosing spondylitis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4. The primary endpoint for both studies was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at Week 14. Both studies included a long-term extension for up to 2 years (**Table 35**).

Table 35. Summary of Patient Demographics for Clinical Trials in Ankylosing Spondylitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (N)[b]	Mean age (SD)	Female (%)	Mean Duration Since Diagnosis (years) (SD)
STUDY AS-I SELECT-AXIS 1 (M16-098)	Randomized, double-blind, multicenter, placebo-controlled, in NSAID-IR[a] bDMARD-naïve patients	RINVOQ 15 mg Placebo orally, once daily Main treatment period: 14 weeks	187	45.4 (12.50)	29	6.9 (8.94)
STUDY AS-II SELECT-AXIS 2 (M19-944 – Study 1)	Randomized, double-blind, multicenter, placebo-controlled, in bDMARD-IR[c] patients	RINVOQ 15 mg Placebo orally, once daily Main treatment period: 14 weeks	420	42.4 (12.08)	26	7.7 (7.52)

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; NSAID = Nonsteroidal Anti-inflammatory Drug, SD = standard deviation

a. Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindication for NSAIDs

b. Includes all randomized patients who received at least one dose of study drug

c. Patients who had an inadequate response or intolerance to one or two bDMARDs

Study AS-I (M16-098) was a 14-week trial in 187 ankylosing spondylitis patients with an inadequate response to at least two NSAIDs or intolerance to or contraindication for NSAIDs and had no previous exposure to biologic DMARDs. At baseline, patients had symptoms of ankylosing spondylitis for an average of 14.4 years and approximately 81% and 16% of the patients were on concomitant NSAID(s) and/or a conventional synthetic (cs) DMARD, respectively. Patients received RINVOQ 15 mg once daily or placebo. At Week 14, all patients randomized to placebo were switched to RINVOQ 15 mg once daily.

Study AS-II (M19-944) was a 14-week trial in 420 ankylosing spondylitis patients with an inadequate response to 1 or 2 biologic DMARDs. At baseline, patients had symptoms of ankylosing spondylitis for an average of 12.8 years and approximately 78% and 31% of the patients were on concomitant

NSAID(s) and/or a csDMARD, respectively. Patients received RINVOQ 15 mg once daily or placebo. At Week 14, all patients randomized to placebo were switched to RINVOQ 15 mg once daily.

Study Results

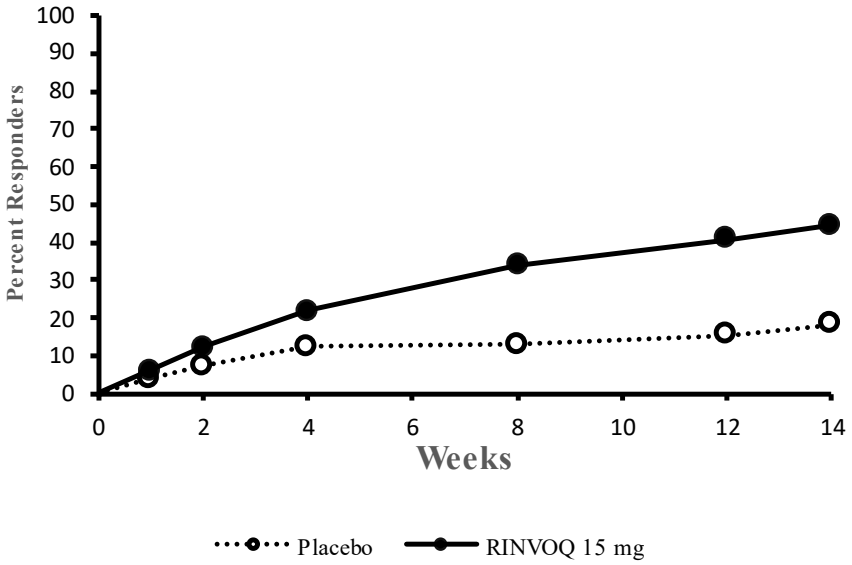
In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (**Figure 3** and **Table 36**). Onset of efficacy was seen as early as Week 2 in Study AS-I and Week 4 in Study AS-II. In Study AS-I, efficacy was maintained through Week 104 as assessed by the endpoints presented in **Table 36**.

Treatment with RINVOQ 15 mg resulted in improvements in individual ASAS components (

Table 37) and other measures of disease activity, including BASDAI and hsCRP compared to placebo at Week 14 (**Table 36**).

Examination of baseline body mass index (BMI), symptom duration of ankylosing spondylitis and baseline hsCRP did not identify differences in response to RINVOQ among these subgroups at Week 14.

Figure 3. Percent of Patients Achieving ASAS40 in Study AS-II*



*Results are based on non-responder imputation in conjunction with multiple imputation.

Table 36. Efficacy results of RINVOQ at Week 14

Efficacy Measure	Study	Study AS-I bDMARD-naïve		Study AS-II bDMARD-IR	
	Treatment Group	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg
	N	94	93	209	211
ASAS40 (% of patients)	Week 14	25.5	51.6[a]	18.2	44.5[a]
ASAS20 (% of patients)	Week 14	40.4	64.5[c]	38.3	65.4[a]
ASAS Partial Remission (% of patients)	Week 14	1.1	19.4[a]	4.3	17.5[a]
BASDAI 50 (% of patients)	Week 14	23.4	45.2[b]	16.7	43.1[a]
ASDAS-CRP	Baseline	3.69	3.52	3.87	3.86
	Week 14	3.07	2.06[a]	3.36	2.32[a]
ASDAS Inactive Disease (% of patients)	Week 14	0	16.1[c]	1.9	12.8[a]
ASDAS Low Disease Activity (% of patients)	Week 14	-	-	10.1	44.1[a]
SPARCC MRI Spine Score	Baseline	12.54	11.24	8.76	11.20
	Week 14	10.06	3.25 [a]	9.16	6.80 [a]
Nocturnal Back Pain	Baseline	6.37	6.43	7.20	7.10
	Week 14	4.56	2.95 [c]	5.63	3.88 [a]

Abbreviations: ASAS20 (or 40) = Assessment of SpondyloArthritis international Society ≥ 20% (or ≥ 40%) improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PBO = placebo; SPARCC MRI = SpondyloArthritis Research Consortium of Canada Magnetic Resonance Imaging

a. multiplicity-controlled p ≤ 0.001 RINVOQ vs placebo comparison

b. multiplicity-controlled p ≤ 0.01 RINVOQ vs placebo comparison

c. nominal p ≤ 0.001 RINVOQ vs placebo comparison

For binary endpoints, Week 14 results are based on non-responder imputation (Study AS-I) and on non-responder imputation in conjunction with multiple imputation (Study AS-II).

Table 37. Components of ASAS Response

Efficacy Measure	Study	Study AS-I bDMARD-naïve		Study AS-II bDMARD-IR	
	Treatment Group	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg
	N	94	93	209	211
Patient Global Assessment of Disease Activity[a]	Baseline	6.8	6.7	7.3	7.4
	Week 14	5.4	3.7[d]	5.9	4.3[d]
Total Back Pain[a]	Baseline	6.7	6.9	7.4	7.5
	Week 14	5.0	3.6[d]	5.9	4.4[c]
BASFI[a]	Baseline	5.64	5.41	6.20	6.25
	Week 14	4.18	3.07[d]	5.09	3.98[c]
Inflammation[b]	Baseline	6.65	6.63	6.73	6.85
	Week 14	4.59	3.37[d]	5.11	3.87[d]

Abbreviations: ASAS = Assessment of SpondyloArthritis international Society; BASFI = Bath Ankylosing Spondylitis Functional Index; PBO = placebo

a. numeric rating scale (NRS): 0 = best, 10 = worst
b. mean of BASDAI questions 5 and 6 assessing morning stiffness severity and duration: 0 = best, 10 = worst
c. multiplicity-controlled $p \leq 0.001$ RINVOQ vs placebo comparison
d. nominal $p \leq 0.001$ RINVOQ vs placebo comparison

Health-Related Outcomes

Improvements were observed as early as Week 1 for total back pain and Week 2 for nocturnal back pain in Study AS-II.

In Study AS-II, patients treated with RINVOQ 15 mg showed significant improvements in health-related quality of life and overall health as measured by ASQoL and ASAS Health Index, respectively, compared to placebo at Week 14. Improvements in ASQoL and ASAS Health Index were also observed in Study AS-I compared to placebo at Week 14.

Enthesitis

In Study AS-II, patients with pre-existing enthesitis treated with RINVOQ 15 mg showed significant improvement in enthesitis compared to placebo as measured by change from baseline in Maastrich Ankylosing Spondylitis Enthesitis Score (MASES) at Week 14. Improvements in MASES were also observed in Study AS-I compared to placebo at Week 14.

Spinal mobility

In Study AS-II, patients treated with RINVOQ 15 mg showed significant improvement in spinal mobility compared to placebo as measured by change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14. Improvements in BASMI were also observed in Study AS-I compared to placebo at Week 14.

Non-radiographic Axial Spondyloarthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in one randomized, double-blind, multicenter, placebo-controlled study in patients 18 years of age or older with active non-radiographic axial spondyloarthritis (**Table 38**). Study SELECT AXIS 2 (Study 2) was a 52-week placebo-controlled trial in

313 patients with active non-radiographic axial spondyloarthritis with an inadequate response to at least 2 NSAIDs or intolerance to or contraindication for NSAIDs (i.e., NSAID-IR). Patients must have had objective signs of inflammation indicated by elevated C reactive protein (CRP) (defined as > upper limit of normal), and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 numerical rating scale (NRS) at the Screening and Baseline Visits.

At baseline, 74.8% and 29.1% of the patients were on a concomitant NSAID or csDMARD, respectively. 32.9% of the patients had an inadequate response or intolerance to bDMARD therapy. Patients received RINVOQ 15 mg once daily or placebo. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at Week 14.

Table 38. Summary of Patient Demographics for Clinical Trial in Non-radiographic Axial Spondyloarthritis

Study #	Trial design	Dosage, route of administration and duration	Study subjects, (N)[a]	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)
SELECT-AXIS 2 (M19-944 – Study 2)	Randomized, double-blind, multicenter placebo-controlled, in NSAID-IR patients	RINVOQ 15 mg Placebo orally, once daily Main treatment period: 52 weeks	313	42.1 (12.21)	58.5	4.4 (5.68)

a. Includes all randomized patients who received at least one dose of study drug.

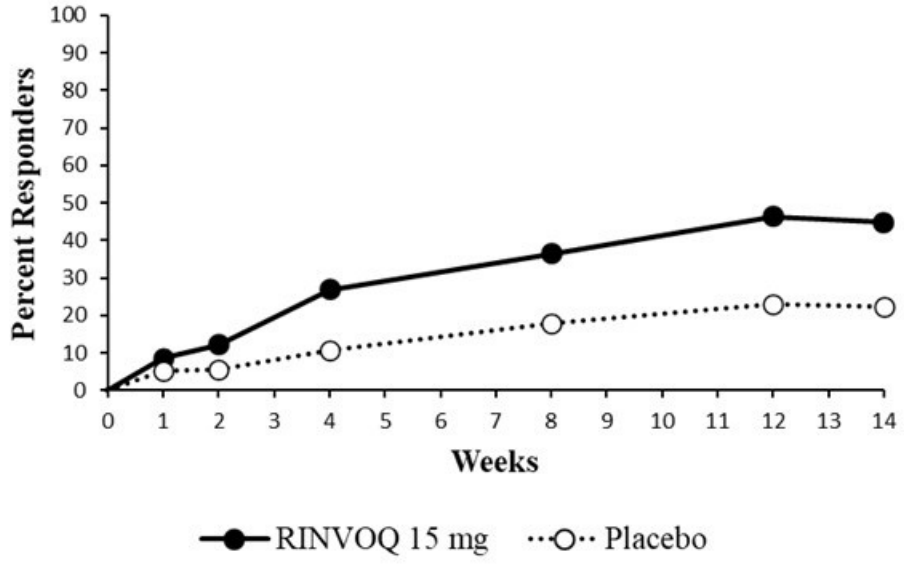
Study Results

In SELECT-AXIS 2, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (**Table 39**, **Figure 1**). Onset of efficacy was seen as early as Week 2 for ASAS40.

Treatment with RINVOQ 15 mg resulted in improvement in individual ASAS components **(Table 40**) and other measures of disease activity, including BASDAI and hsCRP compared to placebo at Week 14.

Examination of baseline BMI, symptom duration of non-radiographic axial spondyloarthritis, baseline hsCRP, MRI sacroiliitis, and prior use of bDMARDs did not identify differences in response to RINVOQ among these subgroups at Week 14.

Figure 4. Percent of Patients Achieving ASAS40*



*Results are based on non-responder imputation in conjunction with multiple imputation.

Table 39. Efficacy Results of RINVOQ at Week 14

Treatment Group		PBO (N = 157)	RINVOQ 15 mg (N = 156)
ASAS40 (% of patients)	Week 14	22.5	44.9[a]
ASAS20 (% of patients)	Week 14	43.8	66.7[a]
ASAS Partial Remission (% of patients)	Week 14	7.6	18.6[b]
BASDAI 50 (% of patients)	Week 14	22.1	42.3[a]
ASDAS-CRP	Baseline	3.61	3.61
	Week 14	2.90	2.22[a]
ASDAS Inactive Disease (% of patients)	Week 14	5.2	14.1[b]
ASDAS Low Disease Activity (% of patients)	Week 14	18.3	42.3[a]
SPARCC MRI score (SI joints)	Baseline	3.49	4.39
	Week 14	3.37	1.90[a]
Nocturnal Back Pain	Baseline	6.98	6.68
	Week 14	5.05	3.74[a]

a. Multiplicity-controlled p≤0.001 RINVOQ vs placebo comparison.

b. Multiplicity-controlled p≤0.01 RINVOQ vs placebo comparison.

For binary endpoints, results are based on non-responder imputation in conjunction with multiple imputation.

Table 40. Components of ASAS Response

Treatment Group		PBO (N = 157)	RINVOQ 15 mg (N = 156)
Patient Global Assessment of Disease Activity[a]	Baseline	7.30	7.03
	Week 14	5.35	4.16[d]
Total Back Pain[a]	Baseline	7.32	7.26
	Week 14	5.27	4.29[c]
BASFI[a]	Baseline	5.97	5.96
	Week 14	4.47	3.33[c]
Inflammation[b]	Baseline	6.68	6.60
	Week 14	4.69	3.48[d]

a. Numeric rating scale (NRS): 0 = best; 10 = worst.
b. Mean of BASDAI questions 5 and 6 assessing morning stiffness severity and duration: 0= best, 10 = worst.
c. Multiplicity-controlled p ≤ 0.001 RINVOQ vs placebo comparison.
d. Nominal p ≤ 0.001 RINVOQ vs placebo comparison.

Health-Related Outcomes

Patients treated with RINVOQ 15 mg showed significant improvements in health-related quality of life and overall health as measured by Ankylosing Spondylitis Quality of Life (ASQoL) and ASAS Health Index, respectively, compared to placebo at Week 14.

Atopic Dermatitis

The efficacy and safety of RINVOQ 15 mg and 30 mg once daily were assessed in 2584 patients (12 years of age and older) from three Phase 3 randomized, double-blind, multicenter studies (**Table 41**).

The study subjects included 344 adolescent and 2240 adult patients with refractory moderate to severe atopic dermatitis (AD) not adequately controlled by topical medication(s). The majority of the study subjects had been treated with systemic therapy or phototherapy prior to initiating RINVOQ treatment. At baseline, patients had to have all the following: an Investigator's Global Assessment (vIGA-AD) score ≥ 3 in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥ 16 (composite score assessing extent and severity of erythema, edema/papulation, scratches and lichenification across 4 different body sites), a minimum body surface area (BSA) involvement of ≥ 10%, and weekly average Worst Pruritus Numerical Rating Scale (NRS) ≥ 4.

In all three studies, patients received RINVOQ once daily at doses of 15 mg or 30 mg or matching placebo for 16 weeks. In two of the studies (Measure Up 1 and Measure Up 2), RINVOQ was used as monotherapy, whereas in the third study, AD UP, patients also received concomitant topical corticosteroids (TCS). Following completion of the double blinded period, patients originally randomized to RINVOQ were to continue receiving the same dose until Week 136. Patients in the placebo group were re-randomized in a 1:1 ratio to receive RINVOQ 15 mg or 30 mg until Week 136.

All three studies assessed the co-primary endpoints of the proportion of subjects with a vIGA-AD 0 (clear) or 1 (almost clear) with at least a 2-point improvement and the proportion of subjects with EASI 75 (improvement of at least 75% in EASI score from baseline) at Week 16.

Key secondary endpoints included EASI 90 and EASI 100 at Week 16 and the proportion of subjects with reduction in itch (≥ 4-point improvement in the Worst Pruritus NRS from baseline) at Week 16 and other timepoints. In the monotherapy studies, key secondary endpoints included worsening of disease (EASI increase ≥ 6.6 points during double-blind period) and the proportion of subjects from baseline to Week 16 with reduction in: symptoms severity (≥ 28-point improvement in the Atopic Dermatitis Symptoms Scale [ADerm-SS] 7-item total symptom score [TSS-7]); symptom frequency (≥ 12-point improvement in the Patient Oriented Eczema Measure); skin pain (≥ 4-point improvement in the ADerm-SS Skin Pain); health-related quality of life (≥4-point improvement in the Dermatology Life Quality Index [DLQI]; DLQI 0/1); the impact of AD related to sleep (≥ 12-point improvement in the Atopic Dermatitis Impact Scale [ADerm-IS] Sleep), daily activities (≥ 14-point improvement in the ADerm-IS Daily Activities), and emotional state (≥ 11-point improvement in the ADerm-IS Emotional State) ; and anxiety and depression symptoms (Hospitalization Anxiety and Depression Scale scores < 8 for both subscales).

Table 41. Summary of Patient Demographics for Clinical Trials in Atopic Dermatitis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)[a]	Age (years) Mean (Range)	Female (%)	Mean Disease Duration (years) (SD)[b]
MEASURE-UP 1 (M16-045)	Randomized, double-blind, placebo-controlled, multicenter, in moderate to severe AD patients Monotherapy	RINVOQ 15 mg RINVOQ 30 mg Placebo Tablets, orally, once daily Main treatment period: 16 weeks	847	34.0 (12-75)	46.2	20.7 (15.14)
MEASURE-UP 2 (M18-891)	Randomized, double-blind, placebo-controlled, multicenter, in moderate to severe AD patients Monotherapy	RINVOQ 15 mg RINVOQ 30 mg Placebo Tablets, orally, once daily Main treatment period: 16 weeks	836	33.6 (12-75)	43.7	20.2 (13.75)
AD UP (M16-047)	Randomized, double-blind, placebo-controlled, multicenter, in moderate to severe AD patients Combination Therapy with TCS	RINVOQ 15 mg plus TCS RINVOQ 30 mg plus TCS Placebo plus TCS Tablets, orally, once daily Main treatment period: 16 weeks	901	34,1 (12-75)	39.3	23.4 (15.09)

Abbreviations: AD = atopic dermatitis, SD = standard deviation, TCS = topical corticosteroids

a. Number of subjects randomized
b. Years since AD diagnosis

Study Results

Clinical Response

RINVOQ demonstrated consistent responses in the co-primary and key secondary endpoints across all three studies. Both the co-primary, as well as all key secondary endpoints were multiplicity-controlled and achieved statistical significance vs placebo ($p < 0.001$).

Monotherapy Studies (MEASURE UP 1 AND MEASURE UP 2)

In the MEASURE UP studies, a significantly greater proportion of patients treated with RINVOQ 15 mg or 30 mg compared to placebo achieved vIGA-AD 0 or 1 response and EASI 75 at Week 16 (**Table 42**)

Table 42. Efficacy Results of RINVOQ Monotherapy Studies at Week 16 (co-primary endpoints)

Study	**MEASURE UP 1**			**MEASURE UP 2**		
Treatment Group	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**
Number of subjects randomized	**281**	**281**	**285**	**278**	**276**	**282**
% responders						
vIGA-AD 0/1[a,b]	8.4	48.1[c]	62.0[c]	4.7	38.8[c]	52.0[c]
EASI 75[a]	16.3	69.6[c]	79.7[c]	13.3	60.1[c]	72.9[c]

Abbreviations: PBO = placebo

a. Based on number of subjects randomized

b. Responder was defined as a patient with vIGA-AD 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on a 0-4 ordinal scale

c. Multiplicity-controlled $p < 0.001$ RINVOQ vs placebo comparison

Table 43. Efficacy Results of RINVOQ Monotherapy Studies at Week 16 (key secondary endpoints)

Study	MEASURE UP 1			MEASURE UP 2		
Treatment Group	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**	**PBO**	**RINVOQ 15 mg**	**RINVOQ 30 mg**
Number of subjects randomized	**281**	**281**	**285**	**278**	**276**	**282**
% responders						
EASI 90[a]	8.1	53.1[d]	65.8[d]	5.4	42.4[d]	58.5[d]
EASI 100[a]	1.8	16.7[d]	27.0[d]	0.7	14.1[d]	18.8[d]
Worst Pruritus NRS[b] *(≥ 4-point improvement)*	11.8 (N = 272)	52.2[d] (N = 274)	60.0[d] (N = 280)	9.1 (N = 274)	41.9[d] (N = 270)	59.6[d] (N = 280)
Mean % change (SE)						
SCORAD[c]	-32.7 (2.33)	-65.7[d] (1.78)	-73.1[d] (1.73)	-28.4 (2.50)	-57.9[d] (2.01)	-68.4[d] (2.04)

Abbreviations: PBO = placebo; SCORAD = SCORing Atopic Dermatitis

a. Based on number of subjects randomized
b. N = number of patients whose baseline Worst Pruritus NRS is ≥ 4
c. % change = least squares mean percent change relative to baseline
d. Multiplicity-controlled p < 0.001 RINVOQ vs placebo comparison

A rapid improvement in skin clearance (defined as EASI 75 by Week 2) was also achieved for both doses compared to placebo. A significantly greater proportion of patients treated with RINVOQ 15 mg or 30 mg achieved clinically meaningful improvement in itch compared to placebo at Week 16. Rapid improvement in itch (defined as a ≥ 4-point reduction in Worst Pruritus NRS by Week 1) was also achieved for both doses compared to placebo, with differences observed as early as 1 day after initiating RINVOQ 30 mg and 2 days after initiating RINVOQ 15 mg. A significantly smaller proportion of patients treated with RINVOQ 15 mg or 30 mg had a disease flare defined as a clinically meaningful worsening of disease during the initial 16 weeks of treatment compared to placebo.

Figure 5 and **Figure 6** show the proportion of patients achieving an EASI 75 response and the proportion of patients with ≥ 4-point improvement in the Worst Pruritus NRS, respectively, up to Week 16.

Figure 5. Proportion of Patients Achieving an EASI 75 Response in Monotherapy Studies

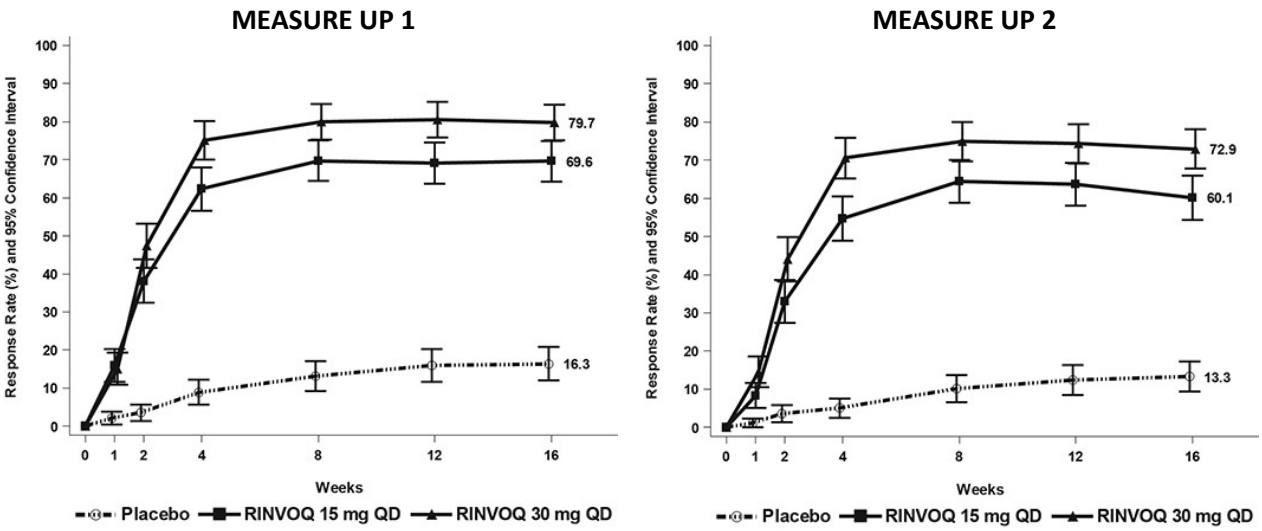
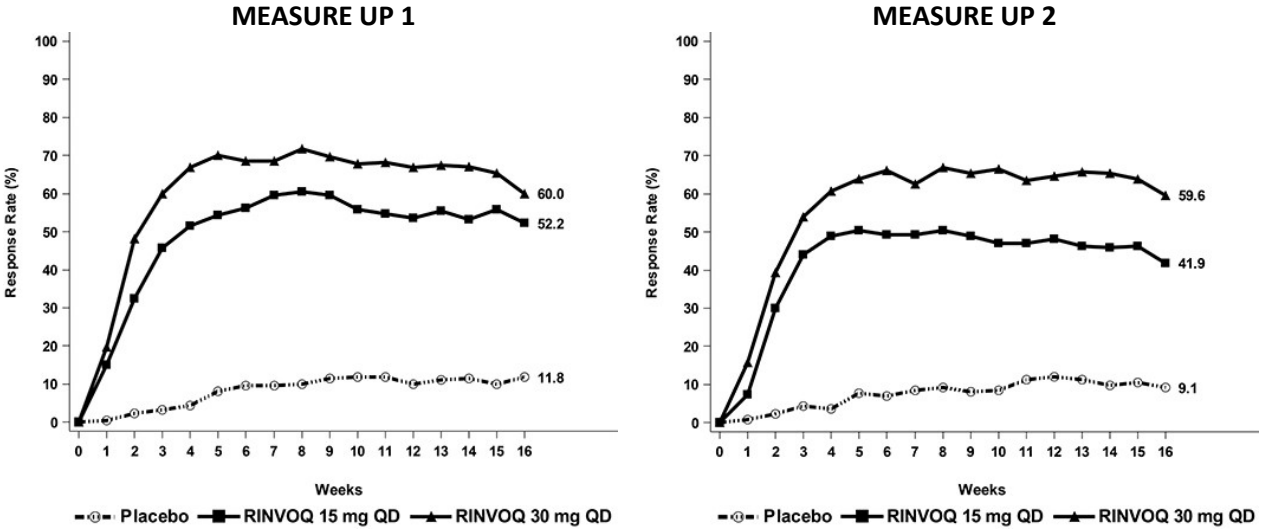


Figure 6. Proportion of Patients with ≥ 4-point Improvement in the Worst Pruritus NRS in Monotherapy Studies



In both studies the efficacy of RINVOQ 15 mg and 30 mg was maintained through Week 52.

Treatment effects in subgroups (weight, age, gender, race, and prior systemic treatment with immunosuppressants) in both studies were consistent with the results in the overall study population.

Concomitant TCS Study (AD UP)

In AD UP, a significantly greater proportion of patients treated with RINVOQ 15 mg + TCS or 30 mg + TCS achieved vIGA-AD 0 or 1 response and EASI 75 compared to placebo + TCS at Week 16 (**Table 44**).

Table 44. Efficacy Results of RINVOQ + Concomitant TCS at Week 16 (co-primary endpoints)

Treatment Group	Placebo + TCS	RINVOQ 15 mg + TCS	RINVOQ 30 mg + TCS
Number of subjects randomized	**304**	**300**	**297**
% responders			
vIGA-AD 0/1[a,b]	10.9	39.6[c]	58.6[c]
EASI 75[a]	26.4	64.6[c]	77.1[c]

Abbreviations: PBO = placebo
a. Based on number of subjects randomized
b. Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
c. Multiplicity-controlled p < 0.001 RINVOQ + TCS vs placebo + TCS comparison

Table 45. Efficacy Results of RINVOQ + Concomitant TCS at Week 16 (key secondary endpoints)

Treatment Group	Placebo + TCS	RINVOQ 15 mg + TCS	RINVOQ 30 mg + TCS
Number of subjects randomized	**304**	**300**	**297**
% responders			
EASI 90[a]	13.2	42.8[d]	63.1[d]
EASI 100[a]	1.3	12.0[e]	22.6[d]
Worst Pruritus NRS[b] *(≥ 4-point improvement)*	15.0 N = 294	51.7[d] N = 288	63.9[d] N = 291
Mean % change (SE)			
SCORAD[c]	-33.6 (1.90)	-61.2[e] (1.70)	-71.0[e] (1.71)

Abbreviations: PBO = placebo
a. Based on number of subjects randomized
b. N = number of patients whose baseline Worst Pruritus NRS is ≥ 4
c. % change = least squares mean percent change relative to baseline
d. Multiplicity-controlled p < 0.001 RINVOQ + TCS vs placebo + TCS comparison
e. Not multiplicity-controlled, nominal p < 0.001 RINVOQ + TCS vs placebo + TCS comparison

A rapid improvement in skin clearance was also achieved for both doses compared to placebo + TCS. In addition, a higher EASI 90 response rate was achieved for both doses at Week 4 compared to placebo + TCS.

A significantly greater proportion of patients treated with RINVOQ 15 mg + TCS or 30 mg + TCS achieved a rapid, and clinically meaningful improvement in itch compared to placebo + TCS.

Figure 7 and **Figure 8** show the proportion of patients achieving an EASI 75 response and the proportion of patients with ≥ 4-point improvement in the Worst Pruritus NRS, respectively up to Week 16.

Figure 7. Proportion of Patients Achieving an EASI 75 Response AD UP Study

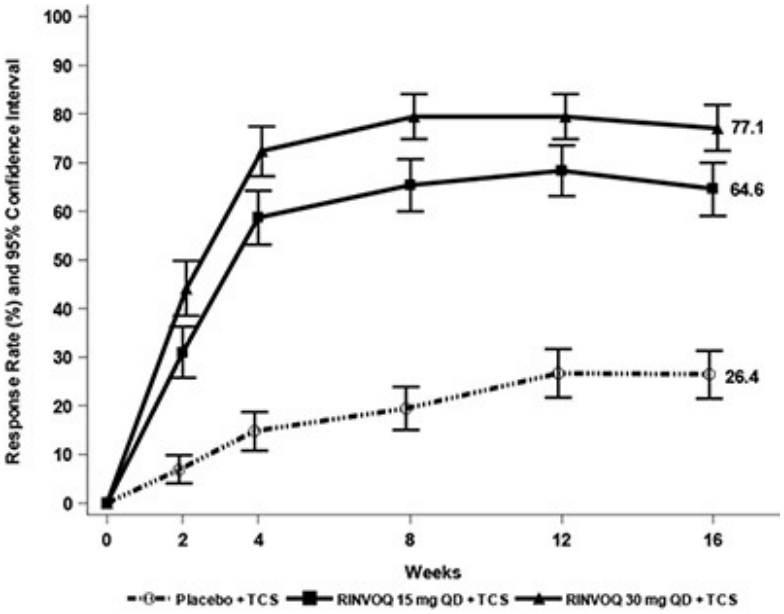
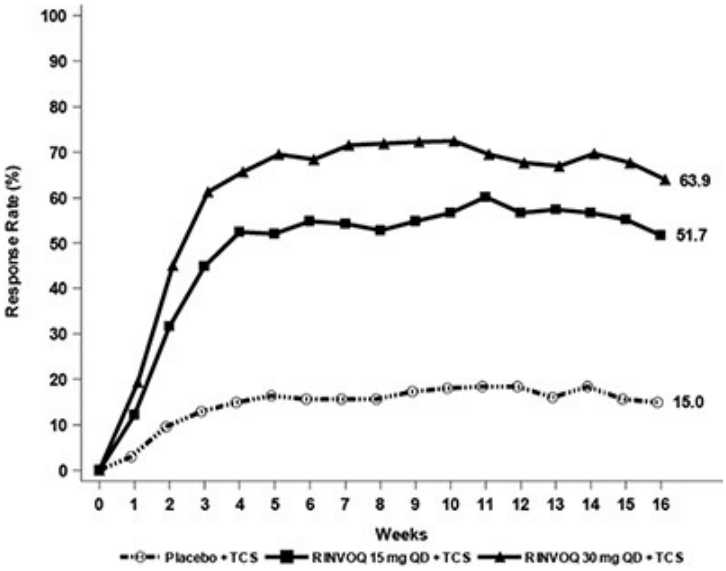


Figure 8. Proportion of Patients with ≥4-point Improvement in the Worst Pruritus NRS in AD UP Study



Treatment effects in subgroups (weight, age, gender, race, and prior systemic treatment with immunosuppressants) in AD UP were consistent with the results in the overall study population.

Results at Week 16 continued to be observed through Week 52 in patients treated with RINVOQ 15 mg + TCS or 30 mg + TCS.

Quality of Life/Patient Reported Outcomes

In the MEASURE UP studies, greater proportions of patients treated with RINVOQ 15 mg and 30 mg versus placebo achieved clinically meaningful reductions in symptom severity, symptom frequency, skin pain, health-related quality of life, and on patient-reported effects on sleep, daily activities, and emotional state. Anxiety and depression symptoms were reduced. All patient-reported outcome comparisons versus placebo at Week 16 were statistically significant for both RINVOQ 15 mg and 30 mg (multiplicity-controlled $p < 0.001$).

Adolescent Population

A total of 344 adolescents aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across the three Phase 3 studies to receive either 15 mg (N = 114) or 30 mg (N = 114) RINVOQ or matching placebo (N = 116), in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the adolescents and adults (**Table 46**). Safety and efficacy of RINVOQ in adolescents weighing less than 40 kg and in patients less than 12 years of age with atopic dermatitis have not been established.

Table 46. Efficacy Results of RINVOQ for Adolescents at Week 16 (Subgroup Results of Co-primary Endpoints)

Study	MEASURE UP 1		MEASURE UP 2		AD UP	
Treatment Group	**PBO**	**RINVOQ 15 mg**	**PBO**	**RINVOQ 15 mg**	**PBO + TCS**	**RINVOQ 15 mg + TCS**
Number of adolescent subjects randomized	**40**	**42**	**36**	**33**	**40**	**39**
% responders						
vIGA-AD 0/1[a,b]	7.5%	38.1%	2.8%	42.4%	7.5%	30.8%
EASI 75[a]	8.3%	71.4%	13.9%	66.7%	30.0%	56.4%

Abbreviations: PBO = placebo

a. Based on number of subjects randomized

b. Responder was defined as a patient with vIGA-AD 0 or 1 (“clear” or “almost clear”) with a reduction of ≥ 2 points on a 0-4 ordinal scale

Table 47. Efficacy Results of RINVOQ for Adolescents at Week 16

Study	MEASURE UP 1		MEASURE UP 2		AD UP	
Treatment Group	**PBO**	**RINVOQ 15 mg**	**PBO**	**RINVOQ 15 mg**	**PBO + TCS**	**RINVOQ 15 mg + TCS**
Number of adolescent subjects randomized	**40**	**42**	**36**	**33**	**40**	**39**
% responders						
Worst Pruritus NRS[a,b] *(≥ 4-point improvement)*	15.4% N = 39	45.0% N = 40	2.8% N = 36	33.3% N = 30	13.2% N = 38	41.7% N = 36

Abbreviations: PBO = placebo

a. N = number of patients whose baseline Worst Pruritus NRS is ≥ 4

b. Subgroup results of ≥ 4-point improvement of Worst Pruritus NRS

Ulcerative Colitis

The efficacy and safety of RINVOQ were evaluated in three multicenter, double-blind, randomised, placebo-controlled Phase 3 clinical studies in patients with moderate to severe ulcerative colitis (UC) who had demonstrated prior treatment failure, i.e., an inadequate response to, loss of response to, or intolerance to at least one of conventional (oral aminosalicylates, corticosteroids, immunosuppressants), and/or biologic (tumour necrosis factor-alpha [TNFα] antagonists, interleukin 12/23 inhibitor or integrin receptor antagonist) therapy. These included two replicate induction studies, UC-1 and UC-2, and a maintenance study, UC-3.

The study population in the pivotal trials consisted of patients aged between 18 and 75 years of age with moderate to severe UC. Disease activity was based on the modified Mayo Score (mMS). The mMS is based on the Mayo scoring system excluding Physician's Global Assessment and ranges from 0 to 9. It consists of three sub-scores, each ranging from 0 (normal) to 3 (most severe): stool frequency subscore (SFS), rectal bleeding subscore (RBS), and a centrally-reviewed endoscopy subscore (ES). Eligible patients had an mMS of 5 to 9 points and an ES of 2 to 3 points (confirmed by central reader) at baseline; an ES of 2 was defined by marked erythema, lack of vascular pattern, friability, and erosions, whereas a score of 3 was defined by spontaneous bleeding and ulceration. Patients with moderate disease had an mMS ≤7, whereas patients with severe disease had an mMS >7.

Table 48. Summary of Patient Demographics for Clinical Trials in Ulcerative Colitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects, N	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)
Induction						
UC-1 U-ACHIEVE Induction M14-234 (Substudy 2)	Randomized, double-blind, placebo-controlled, multicenter study, in patients with[a] or without biologic failure[b]	RINVOQ 45 mg Placebo, Orally, once daily Main treatment period: 8 weeks	473	43.8 (14.22)	37.6	8.8 (7.71)
UC-2 U-ACCOMPLISH M14-675	Randomized, double-blind, placebo-controlled, multicenter study, in patients with[a] or without biologic failure[b]	RINVOQ 45 mg Placebo, Orally, once daily Main treatment period: 8 weeks	515	42.2 (14.59)	37.7	7.3 (6.71)
Maintenance						
UC-3 U-ACHIEVE Maintenance M14-234 (Substudy 3)	Randomized, double-blind, placebo-controlled, multicenter study, in patients with[a] or without biologic failure[b]	RINVOQ 15 mg RINVOQ 30 mg Placebo, Orally, once daily Main treatment period: 52 weeks	451	42.8 (14.38)	41.0	8.6 (7.89)

a. Biologic failure: inadequate response to, loss of response to, or intolerance to prior biologic therapy

b. Without biologic failure: inadequate response, loss of response, or intolerance to conventional therapy but had not failed biologic therapy

Study Results

Induction studies (UC-1 and UC-2)

In studies UC-1 and UC-2, 988 patients (473 and 515 patients, respectively) with moderately to severely active UC were randomized to RINVOQ 45 mg or placebo for 8 weeks with a 2:1 treatment allocation ratio. Disease activity was moderate in 61% and 60% of patients in studies UC-1 and UC-2, respectively.

All enrolled patients had prior treatment failure to conventional and/or biologic treatment. Prior treatment failure to at least 1 biologic therapy was present in 52% and 51% of patients in studies UC-1 and UC-2, respectively. Previous treatment failure to conventional therapy but not biologics was seen in 48% and 49% of patients in studies UC-1 and UC-2, respectively.

At Baseline in studies UC-1 and UC-2, respectively, 39% and 37% of patients received corticosteroids, 1.1% and 0.8% received immunomodulators and 68% and 69% received aminosalicylates. Enrolled patients were permitted to use stable doses of oral aminosalicylates, methotrexate, UC-related antibiotics, and/or oral corticosteroids (up to 30 mg/day prednisone or equivalent). Concomitant biologic therapies, azathioprine, 6-mercaptopurine, intravenous or rectal corticosteroids were prohibited.

The primary endpoint in both studies was clinical remission per mMS, defined as SFS ≤ 1 and not greater than baseline, RBS of 0, and ES ≤ 1 at Week 8. Multiplicity-controlled secondary endpoints included clinical response, endoscopic and histologic improvement, abdominal pain and bowel urgency, and other health related outcomes.

The primary endpoint in the two induction studies was met. A statistically significantly higher proportion of patients in the RINVOQ 45 mg group achieved clinical remission per mMS score at Week 8 compared to placebo (**Table 49**).

Table 49. Proportion of Patients Meeting the Primary Efficacy Endpoint, Clinical Remission at Week 8 in Induction Studies UC-1 and UC-2

UC-1			UC-2		
PBO N = 154	**RINVOQ 45 mg N = 319**	**Treatment Difference (95% CI)**	**PBO N = 174**	**RINVOQ 45 mg N = 341**	**Treatment Difference (95% CI)**
4.8%	26.1%	21.6%* (15.8, 27.4)	4.1%	33.5%	29.0%* (23.2, 34.7)

Abbreviation: PBO = placebo

* p <0.001, adjusted treatment difference (95% CI)

There was a higher proportion of patients treated with RINVOQ 45 mg compared to placebo achieving the primary endpoint both in patients with (UC-1: 17.9% vs 0.4%; UC-2: 29.6% vs 2.4%) and without (UC-1: 35.2% vs 9.2%; UC-2: 37.5% vs 5.9%) prior biologic failure.

RINVOQ 45 mg was statistically significantly superior to placebo for all multiplicity-controlled secondary endpoints.

Table 50. Proportion of Patients Meeting Selected Key Secondary Efficacy Endpoints at Week 8 in Induction Studies UC-1 and UC-2

	UC-1			UC-2		
Endpoint	**PBO N = 154**	**RINVOQ 45 mg N = 319**	**Treatment Difference (95% CI)**	**PBO N = 174**	**RINVOQ 45 mg N = 341**	**Treatment Difference (95% CI)**
Clinical response[a]	27.3%	72.6%	46.3%* (38.4, 54.2)	25.4%	74.5%	49.4%* (41.7, 57.1)
With prior biologic failure[+]	12.8%	64.4%	51.6%	19.3%	69.4%	50.1%
Without prior biologic failure[+]	42.1%	81.8%	39.7%	31.8%	79.8%	48.0%
Endoscopic remission[b]	1.3%	13.7%	12.7%* (8.4, 17.0)	1.7%	18.2%	15.9%* (11.4, 20.3)
With prior biologic failure[+]	0	8.9%	8.9%	1.2%	12.7%	11.6%
Without prior biologic failure[+]	2.6%	19.1%	16.4%	2.4%	23.8%	21.5%
Endoscopic improvement[c]	7.4%	36.3%	29.3%* (22.6, 35.9)	8.3%	44.0%	35.1%* (28.6, 41.6)
With prior biologic failure[+]	1.7%	27.0%	25.3%	4.8%	37.1%	32.3%
Without prior biologic failure[+]	13.2%	46.8%	33.6%	12.0%	51.2%	39.2%
Histologic-endoscopic mucosal improvement (HEMI)[d]	6.6%	30.1%	23.7%* (17.5, 30.0)	5.9%	36.7%	30.1%* (24.1, 36.2)
With prior biologic failure[+]	1.4%	22.7%	21.3%	4.6%	30.7%	26.1%
Without prior biologic failure[+]	11.8%	38.2%	26.4%	7.2%	42.9%	35.7%

Abbreviation: PBO = placebo

[+]The number of patients "With prior biologic failure" in UC-1 and UC-2 are 78 and 89 in the placebo group, and 168 and 173 in the RINVOQ 45 mg group, respectively; the number of patients "Without prior biologic failure" in UC-1 and UC-2 are 76 and 85 in the placebo group, and 151 and 168 in the RINVOQ 45 mg group, respectively.

[*] p <0.001, adjusted treatment difference (95% CI)

a. Per mMS: decrease ≥2 points and ≥30% from Baseline and a decrease in RBS ≥ 1 from Baseline or an absolute RBS ≤1

b. Normalization of the endoscopic appearance of the mucosa, defined as ES of 0

c. ES ≤1 without friability.

d. ES ≤1 without friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations, or granulation tissue).

Rectal Bleeding and Stool Frequency Subscores

The onset of response was assessed using the SFS and RBS (partial modified Mayo Score [pmMS]). Initial response was defined as a decrease of ≥1 point and ≥30% from baseline in pmMS and a decrease in RBS ≥1 or an absolute RBS≤1. Onset of response occurred as early as Week 2 in a greater proportion of patients treated with RINVOQ 45 mg compared to placebo.

Endoscopic and Histologic Assessment

RINVOQ 45 mg achieved endoscopic improvement, endoscopic remission, and histologic endoscopic mucosal improvement at Week 8 both in patients with or without previous biologic failure (see **Table 50**).

Endoscopic remission (ES = 0) with Geboes histologic score < 2.0, indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue was achieved by a greater proportion of patients treated with RINVOQ 45 mg compared to placebo at Week 8 (UC-1: 10.7% vs 1.3%, UC-2: 13.5% vs 1.7%).

Abdominal Pain and Bowel Urgency

A greater proportion of patients treated with RINVOQ 45 mg compared to placebo had no abdominal pain (UC-1: 47% vs 23%, UC-2: 54% vs 24%) and no bowel urgency (UC-1: 48% vs 21%, UC-2: 54% vs 26%) at Week 8.

Other Health Related Outcomes

In both induction studies, patients receiving RINVOQ 45 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score, and quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ), at Week 8 compared to placebo.

Maintenance Study (UC-3)

The efficacy analysis for UC-3 evaluated 451 patients who had achieved clinical response per mMS, defined as mMS decrease ≥2 points and ≥30% from Baseline and a decrease in RBS ≥ 1 from Baseline or an absolute RBS ≤1, following 8-week RINVOQ 45 mg induction treatment. Patients were randomized in a 1:1:1 ratio to receive RINVOQ 15 mg, 30 mg, or placebo for up to 52 weeks.

The primary endpoint was clinical remission per mMS at Week 52. Multiplicity-controlled secondary endpoints included maintenance of clinical remission, corticosteroid-free clinical remission, endoscopic improvement, histologic endoscopic mucosal improvement and other health related outcomes.

The primary endpoint was met since the proportion of patients who had clinical remission at Week 52 was statistically significantly higher in the patients treated with 15 mg RINVOQ and 30 mg RINVOQ, compared to placebo (**Table 51**).

Table 51. Proportion of Patients Meeting the Primary Efficacy Endpoint, Clinical Remission at Week 8 in Induction Studies UC-1 and UC-2 at Week 52 in Maintenance Study UC-3

PBO N = 149	RINVOQ 15 mg N = 148	RINVOQ 30 mg N = 154	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
12.1%	42.3%	51.7%	30.7%* (21.7, 39.8)	39.0%*(29.7, 48.2)

Abbreviation: PBO = placebo

*p <0.001, adjusted treatment difference (95% CI)

The clinical remission rate was numerically higher in patients treated with RINVOQ 30 mg and did not depend on prior biologic treatment failure. The proportion of patients with prior biologic failure meeting the primary efficacy endpoint was 40.5% with RINVOQ 15 mg, 49.1% with RINVOQ 30 mg, vs 7.5% with

placebo. Similarly, higher proportion of patients without prior biologic failure treated with RINVOQ achieved clinical remission (RINVOQ 15 mg: 43.9%, RINVOQ 30 mg: 54.0% vs 17.6% in placebo).

RINVOQ 15 mg and 30 mg were statistically significantly superior to placebo for all multiplicity-controlled ranked secondary endpoints.

Table 52. Proportion of Patients Meeting Selected Secondary Efficacy Endpoints at Week-52 in Maintenance Study UC-3

Endpoint	PBO N = 149	RINVOQ 15 mg N = 148	RINVOQ 30 mg N = 154	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Maintenance of clinical remission[a]	N = 54 22.2%	N = 47 59.2%	N = 58 69.7%	37.4%* (20.3, 54.6)	47.0%* (30.7, 63.3)
With prior biologic failure	N = 22 13.6%	N = 17 76.5%	N = 20 73.0%	62.8%	59.4%
Without prior biologic failure	N = 32 28.1%	N = 30 49.4%	N = 38 68.0%	21.3%	39.9%
Corticosteroid-free clinical remission[b]	N = 54 22.2%	N = 47 57.1%	N = 58 68.0%	35.4%* (18.2, 52.7)	45.1%* (28.7, 61.6)
With prior biologic failure	N = 22 13.6%	N = 17 70.6%	N = 20 73.0%	57.0%	59.4%
Without prior biologic failure	N = 32 28.1%	N = 30 49.4%	N = 38 65.4%	21.3%	37.2%
Endoscopic remission[c]	5.6%	24.2%	25.9%	18.7%* (11.0, 26.4)	19.4%* (11.7, 27.2)
With prior biologic failure[+]	2.5%	21.5%	20.0%	19.0%	17.5%
Without prior biologic failure[+]	9.3%	26.8%	31.2%	17.5%	21.9%
Endoscopic improvement[d]	14.5%	48.7%	61.6%	34.4%* (25.1, 43.7)	46.3%* (36.7, 55.8)
With prior biologic failure[+]	7.8%	43.3%	56.1%	35.5%	48.3%
Without prior biologic failure[+]	22.5%	53.6%	66.6%	31.1%	44.1%
Histologic-endoscopic mucosal improvement[e]	11.9%	35.0%	49.8%	23.8%* (14.8, 32.8)	37.3%* (27.8, 46.8)
With prior biologic failure[+]	5.2%	32.9%	47.6%	27.7%	42.4%
Without prior biologic failure[+]	20.0%	36.9%	51.8%	16.9%	31.8%

[+]The number of patients "With prior biologic failure" are 81, 71, and 73 in the placebo, RINVOQ 15 mg, and 30 mg group, respectively. The number of patients "Without prior biologic failure" are 68, 77, and 81 in the placebo, RINVOQ 15 mg, and 30 mg group, respectively.

[*]p <0.001, adjusted treatment difference (95% CI)

a. Clinical remission per mMS at Week 52 among patients who achieved clinical remission at the end of the induction treatment

b. Clinical remission per mMS at Week 52 and corticosteroid-free for ≥90 days immediately preceding Week 52 among patients who achieved clinical remission at the end of the induction treatment

c. ES subscore = 0

d. ES ≤1 without friability

e. ES ≤1 without friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations, or granulation tissue

Disease Activity and Symptoms

For patients who achieved clinical remission per mMS at induction, it was sustained at Week 52 by a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg compared to placebo (**Table 51**).

Endoscopic and Histologic Assessment

RINVOQ 15 mg and 30 mg demonstrated endoscopic improvement, endoscopic remission, histologic and endoscopic mucosal improvement at Week 52 both in the patients with or without previous biologic failure (**Table 52**). Endoscopic remission with Geboes histologic score < 2.0 was achieved by a greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo at Week 52 (18% and 19% vs 5%).

In UC-3, maintenance of endoscopic improvement at Week 52 (ES ≤1 without friability) was seen in a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg compared to placebo (15 mg: 61.6%, 30 mg: 69.5% vs 19.2%) among patients who achieved endoscopic improvement at the end of induction.

Abdominal Pain and Bowel Urgency

At Week 52, a greater proportion of patients treated with RINVOQ 15 mg and 30 mg compared to placebo had no abdominal pain (15 mg: 46%, 30 mg: 55% vs 21%) and no bowel urgency (15 mg: 56%, 30 mg: 64% vs 17%).

Other Health Related Outcomes

In the maintenance study, patients receiving RINVOQ 15 mg and 30 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score, and quality of life as measured by IBDQ, at Week 52 compared to placebo.

Crohn's Disease

The efficacy and safety of RINVOQ was evaluated in three multicenter, double-blind, placebo-controlled Phase 3 clinical studies: two induction studies, CD-1 (U-EXCEED) and CD-2 (U-EXCEL), followed by a 52-week maintenance treatment and long-term extension study CD-3 (U-ENDURE). The co-primary endpoints were clinical remission and endoscopic response at Week 12 for CD-1 and CD-2, and at Week 52 for CD-3.

Enrolled patients were 18 to 75 years of age with moderately to severely active CD defined as an average daily very soft or liquid stool frequency (SF) ≥ 4 and/or average daily abdominal pain score (APS) ≥ 2, and a centrally-reviewed Simple Endoscopic Score for CD (SES-CD) of ≥ 6, or ≥4 for isolated ileal disease, excluding the narrowing component.

Table 53. Summary of Patient Demographic for Clinical Trials in Crohn's Disease

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)[a]	Age (years) Mean (Range)	Female (%)	Mean Disease Duration (years) (SD)[b]
Induction						
CD-1 U-EXCEED (M14-431)	Randomized, double-blind, placebo-controlled, multicenter, in biologic failure[c] patients	RINVOQ 45 mg Placebo Tablets, orally, once daily Main treatment period: 12 weeks	495	38.1 (18-74)	46.5	11.7 (9.04)
CD-2 U-EXCEL (M14-433)	Randomized, double-blind, placebo-controlled, multicenter, in patients with[c] or without[d] biologic failure	RINVOQ 45 mg Placebo Tablets, orally, once daily Main treatment period: 12 weeks	526	39.6 (18-74)	46.2	8.9 (9.01)
Maintenance						
CD-3 U-ENDURE (M14-430)	Randomized, double-blind, placebo-controlled, multicenter, in patients who achieved clinical response to Studies CD-1 or CD-2	RINVOQ 30 mg RINVOQ 15 mg Placebo Tablets, orally, once daily Main treatment period: 52 weeks	502	37.7 (18-72)	43.6	10.1 (8.77)

Abbreviations: CD = Crohn's Disease, SD = standard deviation

a. Number of subjects randomized and received at least one dose of study drug; in CD-3, the first 502 subjects were included in the primary efficacy analysis
b. Years since CD diagnosis
c. Biologic failure: inadequate response to or intolerance to prior biologic therapy
d. Without biologic failure: inadequate response, or intolerance to conventional therapy but had not failed biologic therapy

Induction Studies (CD-1 and CD-2)

In CD-1 and CD-2, 1021 patients (495 and 526, respectively) were randomized to RINVOQ 45 mg once daily or placebo for 12 weeks with a 2:1 treatment allocation ratio.

In CD-1, all patients had an inadequate response or were intolerant to treatment with one or more biologic therapies (prior biologic failure). Of these patients, 61% (301/495) had inadequate response or were intolerant to two or more biologic therapies.

In CD-2, 45% (239/526) patients had an inadequate response or were intolerant to treatment with one or more biologic therapies (prior biologic failure), and 55% (287/526) had an inadequate response or were intolerant to treatment with conventional therapies but not to biologic therapy (without prior biologic failure).

At baseline in CD-1 and CD-2, 34% and 36% of patients received corticosteroids, 7% and 3% of patients received immunomodulators, and 15% and 25% of patients received aminosalicylates, respectively.

In both studies, patients receiving corticosteroids at baseline initiated a corticosteroid taper regimen starting at Week 4.

Both studies included a 12--week extended treatment period with RINVOQ 30 mg once daily for patients who received RINVOQ 45 mg once daily and did not achieve clinical response per SF/APS (≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily APS and neither greater than baseline) at Week 12.

Study Results

Disease Activity and Symptoms

In CD-1 and CD-2, a significantly greater proportion of patients treated with RINVOQ 45 mg achieved the co-primary endpoint of clinical remission at Week 12 compared to placebo (**Table 54**). In both studies, onset of efficacy was rapid, with a significantly greater proportion of patients treated with RINVOQ 45 mg achieving clinical response 100 (CR-100) as early as Week 2 compared to placebo (**Table 54).** A significantly greater proportion of patients achieved clinical remission at Week 4 compared to placebo (**Table 54**).

A statistically greater proportion of patients treated with RINVOQ 45 mg achieved corticosteroid-free clinical remission compared to placebo at Week 12 in both CD-1 and CD-2 (**Table 54**).

Endoscopic Assessment
In CD-1 and CD-2, a significantly greater proportion of patients treated with RINVOQ 45 mg achieved the co-primary endpoint of endoscopic response at Week 12 compared to placebo (**Table 54**). Improvements were also observed for ulcer-free endoscopy (mucosal healing) in patients treated with RINVOQ 45 mg.

Table 54. Proportion of Patients Meeting Primary and Additional Efficacy Endpoints in Induction Studies CD-1 and CD-2

Study	CD-1 (U-EXCEED)			CD-2 (U-EXCEL)		
Treatment Group	**PBO N = 171**	**UPA 45 mg N = 324**	**Treatment Difference (95% CI)**	**PBO N = 176**	**UPA 45 mg N = 350**	**Treatment Difference (95% CI)**
Co-Primary Endpoints at Week 12						
Clinical remission[a]	14%	40%	26% (19, 33)*	22%	51%	29% (21, 36)*
Prior biologic failure				N=78 14%	N=161 47%	33% (22, 44)
Without prior biologic failure				N=98 29%	N=189 54%	26% (14, 37)
Endoscopic response[b]	4%	35%	31% (25, 37)*	13%	46%	33% (26, 40)*
Prior biologic failure				N=78 9%	N=161 38%	29% (19, 39)
Without prior biologic failure				N=98 16%	N=189 52%	36% (25, 46)
Additional Endpoints at Week 12						
Clinical remission per CDAI[c]	21%	39%	18% (10, 26)*	29%	49%	21% (13, 29)*
Clinical response (CR-100)[d]	27%	51%	23% (14, 31)*	37%	57%	20% (11, 28)*
Corticosteroid-free clinical remission[a,e]	N=60 7%	N=108 37%	30% (19, 41)*	N=64 13%	N=126 44%	33% (22, 44)*
Endoscopic remission[f]	2%	19%	17% (12, 22)*	7%	29%	22% (16, 28)*
Early Onset Endpoints						
Clinical remission at Week 4[a]	9%	32%	23% (17, 30)*	15%	36%	21% (14, 28)*
CR-100 at Week 2[d]	12%	33%	21% (14, 28)*	20%	32%	12% (4, 19)**

Abbreviation: PBO = placebo, UPA = upadacitinib

Note: Studies were powered to determine statistical significance in the overall population, not powered in subgroup of subjects with prior biologic failure or without prior biologic failure.

* $p < 0.001$, adjusted treatment difference (95% CI)

** $p < 0.01$, adjusted treatment difference (95% CI)

*** nominal $p < 0.001$ UPA vs PBO comparison, adjusted treatment difference (95% CI)

a. Average daily very soft or liquid SF ≤ 2.8 and APS ≤ 1.0 and neither greater than baseline
b. Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)
c. CDAI < 150
d. Decrease of at least 100 points in CDAI from baseline
e. Discontinuation of steroid and achievement of clinical remission among patients on steroid at baseline
f. SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable

Other Health Related Outcomes

In CD-1 and CD-2, patients receiving RINVOQ 45 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-Fatigue score, and quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ), at Week 12 compared to placebo.

Maintenance Study (CD-3)

The efficacy analysis for CD-3 evaluated 502 patients who achieved clinical response per SF/APS with the 12-week RINVOQ 45 mg once daily induction treatment. Patients were re-randomized to receive a maintenance regimen of either RINVOQ 15 mg or 30 mg once daily or placebo for 52 weeks, representing a total of at least 64 weeks of therapy.

Disease Activity and Symptoms

A significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg achieved the co-primary endpoint of clinical remission at Week 52 compared to placebo (**Table 55**).
In patients who achieved clinical remission at induction, clinical remission was sustained at Week 52 by a greater proportion of patients treated with RINVOQ 15 mg and 30mg compared to placebo in the maintenance study. Differences in clinical remission rates in patients treated with RINVOQ 15 mg and 30 mg compared to placebo were identified by Week 4 of the maintenance study.

Table 55. Proportion of Patients Meeting Primary and Additional Efficacy Endpoints at Week 52 in Maintenance Study CD-3

Treatment Group	PBO+ N = 165	UPA 15 mg N = 169	UPA 30 mg N = 168	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Co-Primary Endpoints					
Clinical remission[a]	14%	36%	46%	22% (14, 30)*	32% (23, 40)*
Prior biologic failure	N = 126 9%	N = 124 32%	N = 127 43%	24% (14, 33)	34% (24, 44)
Without prior biologic failure	N = 39 33%	N = 45 44%	N = 41 59%	12% (9, 33)	26% (5, 47)
Endoscopic response[b]	7%	28%	40%	21% (14, 28)*	34% (26, 41)*
Prior biologic failure	N = 126 4%	N = 124 23%	N = 127 39%	19% (11, 27)	35% (26, 44)
Without prior biologic failure	N = 39 18%	N = 45 40%	N = 41 44%	22% (3, 41)	26% (7, 45)
Additional Endpoints					
Clinical remission per CDAI[c]	15%	37%	48%	24% (15, 32)*	33% (24, 42)*
Clinical response (CR-100)[d]	15%	41%	51%	27% (18, 36)*	36% (28, 45)*
Corticosteroid-free clinical remission[a,e]	N = 61 5%	N = 63 38%	N = 63 38%	33% (20, 46)*	34% (21, 46)*

Treatment Group	PBO[+] N = 165	UPA 15 mg N = 169	UPA 30 mg N = 168	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Maintenance of clinical remission[a,f]	N = 101 20%	N = 105 50%	N = 105 60%	32% (20, 44)[*]	40% (28, 52)[*]
Endoscopic remission[g]	5%	19%	29%	14% (8, 21)[*]	24% (16, 31)[*]
Clinical remission and endoscopic remission	4%	14%	23%	10% (4, 16)[**]	18% (11, 25)[*]

Abbreviation: PBO = placebo, UPA = upadacitinib

Note: Study was powered to determine statistical significance in the overall population, not powered in subgroup of subjects with prior biologic failure or without prior biologic failure

[+] The placebo group consisted of patients who achieved clinical response per SF/APS with RINVOQ 45 mg at the end of the induction study and were randomized to receive placebo at the start of maintenance therapy

[*] $p < 0.001$, adjusted treatment difference (95% CI)

[**] $p < 0.01$, adjusted treatment difference (95% CI)

[***] nominal $p < 0.001$ UPA vs PBO comparison, adjusted treatment difference (95% CI)

[****] nominal $p < 0.01$ UPA vs PBO comparison, adjusted treatment difference (95% CI)

a. Average daily very soft or liquid SF ≤ 2.8 and APS ≤ 1.0 and neither greater than baseline
b. Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)
c. CDAI < 150
d. Reduction of CDAI ≥ 100 points from baseline
e. Corticosteroid-free for 90 days prior to Week 52 and achievement of clinical remission among patients who were on corticosteroids at induction baseline. Among all patients, 35% in RINVOQ 15 mg group, 45% in RINVOQ 30 mg group, and 14% in placebo were corticosteroid-free for 90 days prior to Week 52 and in clinical remission
f. Defined as achievement of clinical remission at Week 52 in patients who achieved clinical remission at the entry of the maintenance study
g. SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable

Endoscopic Assessment

In CD-3, a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg achieved the co-primary endpoint of endoscopic response at Week 52 compared to placebo (**Table 55)**. Improvements were also observed for ulcer-free endoscopy (mucosal healing) in patients with RINVOQ 15 mg and 30 mg.

Resolution of Extra-intestinal Manifestations

Resolution of extra-intestinal manifestations (e.g., articular, skin, anemia) was observed in a greater proportion of patients treated with RINVOQ 15 mg (25%) and a significantly greater proportion of patients treated with RINVOQ 30 mg (36%) compared to placebo (15%) at Week 52.

Other Health Related Outcomes

In CD-3, patients receiving RINVOQ 30 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-Fatigue score at Week 52 compared to placebo. Patients treated with RINVOQ 15 mg and 30 mg experienced significantly greater improvement from baseline in quality of life, as measured by IBDQ, at Week 52 compared to placebo.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology (single and repeat-dose studies)

In nonclinical studies, decreases in circulating lymphocytes and cellularity of lymphoid tissues, as well as suppression of erythropoiesis, were observed in rats and dogs at clinically relevant doses. In the 39-week dog study, secondary effects related to immunosuppression-induced opportunistic infections, such as demodicosis (mange) in dogs, were observed at exposures approximately two times the expected exposure (AUC) at the clinical dose of 15 mg daily, at similar exposures to those at the clinical dose of 30 mg daily, and at 0.9 times the exposure at the maximum recommended human dose (MRHD) of 45 mg daily, but there were no decreases in circulating lymphocytes and cellularity of lymphoid tissues. Immunotoxicity evaluations in male and female rats revealed complete suppression of IgM and IgG antibody responses to an injected test antigen (keyhole limpet hemocyanin) at all upadacitinib dose levels (5-50 mg/kg/day) in juvenile animals, and a dose-dependent suppression of IgM and IgG responses at all dose levels (5-60 mg/kg/day) in adult rats. The magnitude of the decreases in antibody responses were greater than the decreases in lymphocyte count in rats. The findings in juvenile and adult rats indicated upadacitinib-related suppression of antibody responses, consistent with JAK inhibition.

Carcinogenicity

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the clinical dose of 15 mg, 2 and 5 times the clinical dose of 30 mg, and 1.7 and 4 times the daily MRHD exposure at 45 mg, on an AUC basis for males and female rats, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day, at which systemic exposures to upadacitinib were similar to those expected at the MRHD of 45 mg daily.

Genotoxicity

Upadacitinib was not mutagenic or genotoxic based on the results of an in vitro bacterial mutagenicity assay (Ames assay), an in vitro chromosome aberration assay in human peripheral blood lymphocytes, and an in vivo male rat bone marrow micronucleus assay for gene mutations and chromosomal aberrations.

Reproductive and Developmental Toxicology

Upadacitinib was teratogenic in rats and rabbits when given at exposures of 1.6 and 15 times the clinical dose of 15 mg daily, 0.8 and 7.6 times the clinical dose of 30 mg daily, and 0.6 and 6 times the MRHD of 45 mg daily (on an AUC basis at maternal oral doses of 4 mg/kg/day and 25 mg/kg/day, respectively).

In two rat embryofetal development studies, pregnant animals were dosed orally during the period of organogenesis from gestation day (GD) 6 to GD 17. Upadacitinib was teratogenic at all dose levels studied in rats except the lowest dose of 1.5 mg/kg/day at which systemic exposure to upadacitinib was approximately 0.3 times the exposure at the 15 mg dose, 0.15 times the exposure at the 30 mg dose, and 0.10 times the exposure at the MRHD of 45 mg daily on an AUC basis.

At maternal oral doses of 4, 5, 25, and 75 mg/kg/day, upadacitinib-related effects included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and, at 75 mg/kg/day (at an exposure of approximately 84 times the 15 mg dose, 43 times the 30 mg dose and 31 times the MRHD of 45 mg on an AUC basis), an increase in bent bones of the fore- and hind-limbs in the absence of maternal toxicity. Additionally, at 25 and 75 mg/kg/day, there was an increase in bent ribs, a skeletal variation, which was also considered upadacitinib-related.

In a rabbit embryofetal development study, pregnant animals were dosed orally during the period of organogenesis from GD 7 to GD 19. Upadacitinib was teratogenic when given at 25 mg/kg/day. Developmental effects observed at 25 mg/kg/day in rabbits included an increase in post-implantation losses, increases in total and early resorptions, lower fetal body weights, and increased incidence of cardiac malformations. In addition, maternal toxicity was evident in the 25 mg/kg/day dose group from body weight loss, lower food consumption, and the increased occurrence of aborted pregnancies. Systemic exposure to upadacitinib at the no-effect dose of 10 mg/kg/day was about twice that at the clinical dose of 15 mg daily, at approximately the same exposure as the 30 mg dose daily, and 0.8 times the exposure at the MRHD of 45 mg daily.

In a pre-/postnatal development study in rats, development of the offspring consequent to exposure of the mothers from implantation through lactation and weaning was tested. Because manifestations of effects induced during this period may be delayed, observations were continued through sexual maturity of the pups. Mothers were dosed orally from GD 6 to Lactation Day 20. Upadacitinib had no effects at any dose level (2.5, 5, and 10 mg/kg/day) in mothers or their offspring in behavioral or reproductive endpoints.

In a fertility and early embryonic development study in rats, upadacitinib had no effect on fertility at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females. However, maintenance of pregnancy was adversely affected at oral doses of 25 and 75 mg/kg/day as demonstrated by dose related increases in fetal resorptions associated with post-implantation losses, which were attributed to the developmental/teratogenic effects of upadacitinib in rats. The 5 mg/kg/day dose was the no-effect dose for early embryonic development.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrRINVOQ®

upadacitinib extended-release tablets

Read this carefully before you start taking **RINVOQ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RINVOQ**.

Serious Warnings and Precautions

Serious Infections

- You should not take RINVOQ if you have any kind of infection.
- RINVOQ is a medicine that affects your immune system. It can lower the ability of your body to fight infections. Examples of these types of infection are tuberculosis, shingles (herpes zoster) or cryptococcosis, or infections caused by other bacteria, fungi or viruses that can spread throughout your body.
- In some cases, these infections may lead to hospitalization or death.
- Most patients taking RINVOQ who developed these infections were also taking other medicines, such as methotrexate or corticosteroids. These medicines may have made it harder to fight infections.
- Contact your healthcare professional if you have any signs or symptoms of an infection, such as:
    - fever, sweating, chills,
    - muscle aches,
    - cough,
    - shortness of breath,
    - coughing up blood,
    - weight loss,
    - warm, red, or painful skin or sores on your body,
    - diarrhea or stomach pain,
    - burning when you urinate or urinating more often than normal,
    - feeling very tired.

- Your healthcare professional will monitor you for the signs and symptoms of infection during and after your treatment with RINVOQ.

Cancers

- Lymphoma, skin cancer, and other cancers have been reported in patients treated with RINVOQ.
- Your healthcare professional will closely monitor you for signs and symptoms of cancer and other serious conditions during treatment with RINVOQ.

Blood clots

- Deep vein thrombosis (blood clots in the veins of your legs), pulmonary embolism (blood clots in the lungs) or arterial thrombosis (blood clot in an artery) have occurred in patients taking RINVOQ and other similar medications. These blood clots can be life-threatening and cause death.
- Stop RINVOQ and seek immediate medical help if you develop any signs or symptoms of a blood

clot in your
- leg (such as swelling, pain or tenderness in the leg); or
- lung (such as sudden unexplained chest pain or shortness of breath).

Major heart related problems
- Major heart related problems have been reported in Rheumatoid Arthritis patients treated with other similar medications (Janus kinase inhibitors).
- Talk to your healthcare professional about possible heart disease risk factors before taking RINVOQ.
- Stop RINVOQ and seek immediate medical help if you develop symptoms of a heart problem such as heart attack or stroke. See the **Serious side effects and what to do about them Table**, below, for the symptoms related to these conditions.

What is RINVOQ used for?

RINVOQ is used to treat:

- adults with rheumatoid arthritis when treatment with methotrexate has not worked well or was not tolerated well. RINVOQ may be taken alone or in combination with other medicines.
- adults with psoriatic arthritis when treatment with other medicines have not worked well or were not tolerated well. RINVOQ may be taken alone or in combination with methotrexate.
- adults with active axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) when treatment with other medicines have not worked well or are not appropriate. Axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) is a disease that primarily causes inflammation in the spine. RINVOQ may be taken alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs).
- adults and adolescents 12 years of age and older and weighing 40 kg or more with refractory moderate to severe eczema (atopic dermatitis). It is used when treatment with other medications has not worked well or was not tolerated well. RINVOQ may be used with or without topical corticosteroids.
- adults with ulcerative colitis when treatment with other medicines has not worked well or was not tolerated well.
- adults with Crohn's disease when treatment with other medicines have not worked well or were not tolerated well.

How does RINVOQ work?

RINVOQ is a 'Janus kinase' (JAK) inhibitor. JAK is an enzyme in your body, which normally helps to turn on your immune system when you need it. However, when it is too active this can also lead to inflammation that could result in swelling, redness and/or pain.

RINVOQ works by attaching to the JAK enzyme to lower its activity.

Rheumatoid arthritis

In people with rheumatoid arthritis, RINVOQ can help to reduce inflammation and improve signs and symptoms like tenderness and pain in and around their joints. It can help to slow down damage to the bone and joints.

Psoriatic arthritis

In people with psoriatic arthritis, RINVOQ can help to reduce inflammation and improve signs and symptoms like pain, stiffness, and swelling in and around their joints, psoriatic skin rash, and tiredness. It can help to slow down damage to the bone and joints.

Axial spondyloarthritis (axSpA)

- Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

  In people with ankylosing spondylitis, RINVOQ can help to reduce inflammation and improve signs and symptoms like back pain, including at night, and stiffness. These effects can help you to improve your health-related quality of life.

- Non-radiographic axial spondyloarthritis (nr-axSpA)

  In people with non-radiographic axial spondyloarthritis, RINVOQ can help to reduce inflammation and improve signs and symptoms like back pain, including back pain at night, and stiffness. These effects can help you to improve your health-related quality of life.

Eczema (Atopic Dermatitis)

In people with eczema who experience inflammation, RINVOQ can improve the condition of your skin, and reduce itching, flares, overall symptoms of eczema, and the impact of eczema on your quality of life.

Ulcerative colitis

In people with ulcerative colitis, RINVOQ can help to control inflammation in the large intestine. RINVOQ can improve signs and symptoms like abdominal pain, rectal bleeding, and the need to rush to and the number of times you go to the toilet. It can help you do normal daily activities and improve your health-related quality of life.

Crohn's Disease

In people with Crohn's disease RINVOQ helps to control inflammation of your intestinal lining. RINVOQ can improve signs and symptoms like frequent and loose stools, and abdominal pain. It can help you do normal daily activities, reduce fatigue, and improve your health-related quality of life.

What are the ingredients in RINVOQ?

Medicinal ingredient: upadacitinib (as upadacitinib hemihydrate)

Non-medicinal ingredients: black iron oxide (E172)/ferrosoferric oxide (15 mg only), hypromellose, iron oxide red (E172), iron oxide yellow (E172) (45 mg only), macrogol/polyethylene glycol, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, silica (colloidal anhydrous)/colloidal silicon dioxide, talc, tartaric acid, and titanium dioxide (E171). The tablets are gluten-free.

RINVOQ comes in the following dosage forms:

Extended-release tablets: 15 mg, 30 mg, and 45 mg upadacitinib

Do not use RINVOQ if:

- you are allergic to upadacitinib or any of the other ingredients in RINVOQ.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RINVOQ. Talk about any health conditions or problems you may have, including if you:

- have or have had tuberculosis (TB).
  - You may need tests to check for TB before you are given RINVOQ.
  - Tell your healthcare professional if you get a persistent cough, fever, night sweats and weight loss during RINVOQ treatment. These can be signs of TB.
- have had a herpes infection (shingles).
  - This is because RINVOQ may allow it to come back.
  - Tell your healthcare professional if you get a painful skin rash with blisters during RINVOQ treatment. These can be signs of shingles.
  - If you are of Asian descent, this may increase your risk of having shingles.
- have or have had liver problems or hepatitis B or C.
- have recently had or plan to have a vaccination (immunization). You should not be given certain types of vaccines while using RINVOQ.
- have or have had cancer, you smoke or have smoked in the past. Your healthcare professional will decide if you can still be given RINVOQ.
- are at high risk of developing skin cancer, or if you develop a new lesion or any change in the appearance of an area on the skin.
- have or have had heart problems, or heart disease risk factors, such as if you
  - have high blood pressure,
  - have high cholesterol.
  - are a smoker, or were a smoker in the past.
- have unexplained stomach (abdominal) pain
- have or have had diverticulitis (inflammation in parts of your large intestine), or gastrointestinal perforation (tears in your stomach or intestine).
  - Some people taking RINVOQ can get tears in their stomach or intestines.
  - Patients taking medications called non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids or those who have diverticulitis are more likely to have a gastrointestinal perforation.
- have low blood cell counts.
  - Treatment with RINVOQ can be associated with anemia (low red blood cells), neutropenia or lymphopenia (low white blood cells).
- have muscle pain and / or muscle weakness.
- have severe kidney problems or worsening of previous kidney problems.

Other warnings you should know about:

Blood tests

You may need blood tests before you start RINVOQ. These tests may be repeated while you are taking RINVOQ. These will help your healthcare professional to know how RINVOQ is affecting your blood and how well your liver is working.

Pregnancy and breastfeeding

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking this medicine. You should not use RINVOQ if you are pregnant.
- Avoid becoming pregnant while taking RINVOQ. It may harm your unborn baby. Use effective birth control while you are taking RINVOQ, and for at least 4 weeks after your last dose of RINVOQ. If you become pregnant during this time, tell your healthcare professional right away.
- You should not use RINVOQ if you are breastfeeding. It is not known if RINVOQ passes into breast milk. You and your healthcare professional should decide if you will take RINVOQ or breastfeed. Talk to your healthcare professional about the best way to feed your baby while you are being treated with RINVOQ.

Adults aged 65 years and older

Side effects, including serious side effects, have occurred more often in patients aged 65 years and older.

If you are 65 years of age or older you may be more at risk of infections, heart problems (including heart attack), and some types of cancer. Your doctor will discuss with you if treatment with RINVOQ is right for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RINVOQ:

- medications for fungal infections (such as ketoconazole, itraconazole, posaconazole or voriconazole).
- a medication to treat bacterial infections called clarithromycin.
- a medication to treat bacterial infections like TB called rifampicin.
- a medication to prevent seizures called phenytoin.
- medications that affect your immune system (such as azathioprine, cyclosporin, and tacrolimus).
- medications that may increase your risk of gastrointestinal perforations, which are tears in the stomach or intestine wall (such as non-steroidal anti-inflammatory medicines, opioids, and corticosteroids)
- an herbal remedy used mainly for depression called St-John's Wort (hypericum perforatum).
- products or juices containing grapefruit. Avoid eating or drinking any products or juices containing grapefruit while taking RINVOQ.

These products may affect the amount of RINVOQ in your blood.

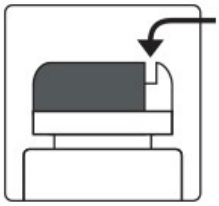
How to take RINVOQ:

- Take exactly as your healthcare professional tells you.
- Take once per day with or without food.
- Swallow tablets whole with water at about the same time each day.
- Do NOT split, crush or chew the tablets.
- Do not change your dose.
- Do not stop taking RINVOQ without first talking with your healthcare professional.

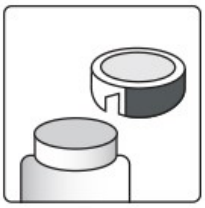
Your healthcare professional may prescribe RINVOQ alone or in combination with other medication. If you receive treatment with another drug, your healthcare professional will tell you how to take it. Be sure to read the package leaflet for the other drug as well as this one. The AbbVie Care Patient Support Program (1 866-848-6472) is also available to you if you have any questions regarding your treatment.

How to open the bottle and puncture the foil:

RINVOQ tablets will be given to you in bottles. Each bottle is sealed with foil and then closed with a cap. The cap has a cutting tool that can be used to help you puncture the foil seal.

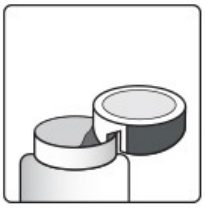


1. The cap of the RINVOQ bottle has a foil cutting tool.



2a. To remove the cap from the bottle, push down and (at the same time) turn the cap counterclockwise.

2b. Turn the cap over. Place the cutting tool near the edge of the foil seal.



3. Push down to make a hole in the foil. Move the cutting tool around the edge of the foil. This will cut the foil all the way around.

4. When you have taken your tablet, put the cap back on and close the bottle.

Usual dose:

Rheumatoid Arthritis, Psoriatic Arthritis, Axial Spondyloarthritis (Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis):

Adults (18 years of age or older): The recommended dose is one 15 mg tablet once a day.

Eczema:

Adolescents (12 years of age and older weighing at least 40 kg): The recommended dose is one 15 mg tablet once a day.

Adults (18 to 64 years of age): The recommended dose is one 15 mg tablet once a day.

Your doctor may prescribe one 30 mg tablet once a day, if necessary.

Adults (65 years of age or older): The recommended dose is one 15 mg tablet once a day.

Ulcerative Colitis

Adults (18 to 64 years of age): The recommended oral dose is one 45 mg tablet once a day for 8 weeks. After 8 weeks, this will be followed by one 15 mg or one 30 mg tablet once a day for your long-term treatment.

Adults (65 years of age or older): The recommended oral dose is one 45 mg tablet once a day for 8 weeks. After 8 weeks, this will be followed by one 15 mg tablet once a day for your long-term treatment.

Crohn's Disease:

Adults (18 to 64 years of age): The recommended oral induction dose of RINVOQ is 45 mg once daily for 12 weeks. After 12 weeks, this will be followed by one 15 mg or 30 mg tablet once a day for your long-term treatment.

Adults (65 years or older): The recommended oral induction dose of RINVOQ is 45 mg once daily for 12 weeks. After 12 weeks, the recommended oral maintenance dose is 15 mg once a day for your long-term treatment.

Your healthcare professional may interrupt your treatment with RINVOQ if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much RINVOQ, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of RINVOQ, take your dose as soon as you remember as long as it is **at least 10 hours before your next dose**. DO NOT take more than 1 tablet per day.
- If you forget your dose for an entire day, skip the missed dose and take only a single dose as usual the following day.
- Do NOT take a double dose to make up for a forgotten dose.

What are possible side effects from using RINVOQ?

These are not all the possible side effects you may have when taking RINVOQ. If you experience any side effects not listed here, tell your healthcare professional.

- throat and nose infections
- cough
- headache
- nausea
- cold sores
- back pain
- acne
- weight gain

If you have eczema, you may also get the following side effects:

- inflammation (swelling) of the hair follicles
- flu (influenza)
- pain in your belly (abdomen)
- fatigue (feeling unusually tired and weak)

If you have ulcerative colitis, you may also get the following side effects:

- rash

RINVOQ can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bronchitis (inflammation in the lung): persistent cough with or without mucus, fatigue, shortness of breath		✓	
Herpes Zoster (shingles): painful skin rash with blisters and fever			✓
Pneumonia (lung infection): coughing, fever, fatigue		✓	
UNCOMMON			
Anemia (low red blood cells): shortness of breath, feeling very tired, pale skin, fast heartbeat, loss of energy, weakness		✓	
Cellulitis (skin infection): redness, swelling, painful skin		✓	
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): swelling, pain, arm or leg may be warm to the touch and may appear red			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Fever		✓	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, itching			✓
Osteoarthritis (wear and tear arthritis): pain, swelling, and stiffness in joints		✓	
Pulmonary embolism (blood clot in the lung): sharp chest pain, coughing up blood, sudden shortness of breath			✓
Urinary tract infection: difficulty or increased need to urinate, pain or burning sensation when peeing, pain in the pelvis or middle of the back, urine that is cloudy or bloody		✓	
RARE			
Arterial thrombosis (blood clot in an artery): chest pain, shortness of breath, dizziness, face drooping on one side, weakness in one arm, slurred speech, limbs may become painful, skin on limb may be pale or blue in colour and cold			✓
Gastrointestinal perforation (tear in the stomach or intestinal wall): abdominal pain, feeling sick, vomiting, constipation, fever			✓
Hypercholesterolemia/hyperlipidemia (high cholesterol)		✓	
Increased Creatine Phosphokinase (CPK; CPK is an enzyme found in the blood when there is muscle damage): muscle aches, pain, or stiffness; muscle weakness	✓		
Neutropenia, leukopenia or lymphocytopenia (low white blood cells): fever or infection, fatigue, aches and pains, flu-like symptoms, swollen lymph nodes, painful joints		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Major Heart Related Problems such as Heart Attack and Stroke: shortness of breath, discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back, severe tightness, pain, pressure, or heaviness in your arms, back, stomach, chest, throat, neck, or jaw, breaking out in cold sweat, nausea or vomiting, feeling lightheaded, weakness in one part or on one side of your body and slurred speech.			✓
Oral candidiasis (thrush in the mouth): thick white patches in the mouth, tongue or on the throat, sore throat		✓	
Skin cancer: new skin lesions during or after therapy or if an existing lesion changes appearance		✓	
Cancers involving different body organs		✓	
UNKNOWN FREQUENCY			
Allergic reactions (trouble breathing, chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue or throat, hives)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 2 to 25°C in the original bottle with the desiccant to protect from moisture.

Keep out of reach and sight of children.

Do not use this medicine after the expiration date which is stated on the carton after 'EXP'.

If you want more information about RINVOQ:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.abbvie.ca), or by calling 1-888-704-8271.
- Additional guidance and support can be obtained by calling the AbbVie Care Support Program at 1-866-848-6472.

This leaflet was prepared by AbbVie Corporation.

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