▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

WARNINGS:
Based on the results from a post-marketing safety study of another JAK inhibitor, RINVOQ should only be used if no suitable treatment alternatives are available in patients:

- **With history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers).**
- **With malignancy risk factors (e.g. current malignancy or history of malignancy).**
- **Who are 65 years of age and older.**

See Section 4.4 Special Warnings and Precautions for Use: Mortality; Major Adverse Cardiovascular Events (MACE); Thrombosis, Malignancy, Non-melanoma Skin Cancer and Use in the Elderly.

AUSTRALIAN PRODUCT INFORMATION – RINVOQ®

UPADACITINIB - TABLET

1 NAME OF THE MEDICINE

Upadacitinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ contains upadacitinib hemihydrate, equivalent to 15 mg, 30 mg, or 45 mg of upadacitinib, a Janus Kinase (JAK) inhibitor.

The tablets do not contain gluten or lactose.

For the full list of excipients, see Section **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

RINVOQ 15 mg modified release tablets are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side.

RINVOQ 30 mg modified release tablets are red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side.

RINVOQ 45 mg modified release tablets are yellow to mottled yellow, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a45’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis

RINVOQ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs (DMARDs).

RINVOQ may be used as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

Psoriatic Arthritis

RINVOQ is indicated for the treatment of moderate to severe active psoriatic arthritis in adult patients who have responded inadequately to, or are intolerant to one or more DMARDs.

RINVOQ may be used as monotherapy or in combination with a non-biological DMARD.

Non-radiographic Axial Spondyloarthritis

RINVOQ is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) change, who have responded inadequately to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ankylosing Spondylitis

RINVOQ is indicated for the treatment of adults with active ankylosing spondylitis.

Atopic Dermatitis

RINVOQ is indicated for use in adults and adolescents aged 12 years and above who weigh at least 40 kg, for the treatment of moderate to severe atopic dermatitis which is inadequately controlled with active topical pharmacotherapies and for whom systemic therapy is indicated.

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis, who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biological medicine.

Crohn's Disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease, who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biological medicine.

4.2 Dose and method of administration

Therapy with RINVOQ should be initiated and monitored by a specialist physician well versed in the use of immunomodulatory therapeutic agents like RINVOQ with expertise in the management of the indicated conditions.

RINVOQ should not be initiated in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have haemoglobin levels less than 8 g/dL (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS**).

RINVOQ tablets should be taken orally with or without food.

RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

Rheumatoid Arthritis

The recommended dose of RINVOQ is 15 mg once daily.

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

Psoriatic Arthritis

The recommended dose of RINVOQ is 15 mg once daily.

RINVOQ may be used as monotherapy or in combination with a non-biological DMARD.

Non-radiographic Axial Spondyloarthritis

The recommended dose of RINVOQ is 15 mg once daily.

Ankylosing Spondylitis

The recommended dose of RINVOQ is 15 mg once daily.

Atopic Dermatitis

Adults

The recommended starting dose of RINVOQ is 15 mg once daily for adults.

In adults aged less than 65 years, the dose may be increased to 30 mg once daily from 4 weeks after initiation of treatment, if clinically warranted and based on benefit-risk assessment.

The lowest effective dose for maintenance should be considered.

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.

RINVOQ should be ceased if a satisfactory clinical response is not achieved after 16 weeks.

Ulcerative Colitis

Induction

The recommended induction dose of RINVOQ is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by Week 8, RINVOQ 45 mg once daily may be continued for an additional 8 weeks. RINVOQ should be ceased if a satisfactory clinical response is not achieved after 16 weeks.

Maintenance

Use the lowest effective dosage needed to maintain response.

The recommended dose of RINVOQ for maintenance treatment is 15 mg once daily. A dose of 30 mg once daily may be considered for patients with refractory, severe or extensive disease. A dose of 30 mg once daily may be appropriate for patients who do not show a satisfactory clinical response to 15 mg once daily.

RINVOQ should be ceased if a satisfactory clinical response is not achieved with the 30 mg dose.

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

Patients 65 years of age or older

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

Crohn's Disease

Induction

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

For patients who have not achieved adequate therapeutic benefit after the initial 12-week induction, RINVOQ may be continued at a dose of 30mg once daily. If there is no evidence of therapeutic benefit after a further 12 weeks (i.e. 24 weeks in total of treatment) RINVOQ should be discontinued.

Maintenance

Use the lowest effective dosage needed to maintain response.

The recommended dose of RINVOQ for maintenance treatment is 15 mg once daily.

For patients who are not at higher risk of venous thromboembolism (VTE), MACE and malignancy (see section 4.4), a dose of 30 mg once daily may be appropriate for:

- patients with refractory, severe or extensive disease or
- patients who do not show a satisfactory clinical response to 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.

In line with clinical best practice, ongoing treatment should be reviewed every 3 to 6 months. RINVOQ should be ceased if a satisfactory clinical response is not achieved with the 30 mg dose.

Patients 65 years of age or older

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

Dose Interruption

RINVOQ treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1.

Table 1. Recommended Dose Interruptions for Laboratory Abnormalities

Laboratory measure	Action
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is <1 x 10^9 cells/L and may be restarted once ANC return above this value
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is <0.5 x 10^9 cells/L and may be restarted once ALC return above this value
Haemoglobin (Hb)	Treatment should be interrupted if Hb is <80 g/L and may be restarted once Hb return above this value
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected

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.

Dosing in Special Populations:

Paediatric Use

Atopic Dermatitis

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.

Rheumatoid Arthritis, Psoriatic Arthritis, Non-radiographic Axial Spondyloarthritis, Ankylosing Spondylitis, Ulcerative Colitis and Crohn's Disease

The safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 18 years have not yet been established. No data are available.

Concomitant use with strong CYP3A4 inhibitors

See section 4.5 Strong CYP3A4 inhibitors for recommended dose adjustments.

Use in the Elderly

Refer to indication specific guidance.

Use in Renal Impairment

No dose adjustment is recommended for patients with stage 2 kidney disease (glomerular filtration rate (GFR) of 60 mL/min/1.73 m^2 or higher). Patients with kidney disease stages 3 to 5 (GFR <60 mL/min/1.73 m^2) may have increased plasma exposures to upadacitinib which may increase potential for adverse events. There are no evaluable data on use of upadacitinib in stage 5 kidney disease (GFR <15 mL/min/1.73 m^2 or on dialysis; see **5.2 PHARMACOKINETIC PROPERTIES**). While the majority of upadacitinib elimination occurs through non-renal clearance, prudent dosing is recommended in patients with kidney disease stages 3 to 5 (see Table 2 for dosing recommendations)

RINVOQ has not been studied in patients with end stage renal disease (eGFR <15mL/min/1.73m^2.

Table 2. Recommended Dose in Renal Impairment

Stages	Indication	Recommended once daily dose
Stage 3 **(GFR 30 - 60 mL/min/1.73 m^2)**	Rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, atopic dermatitis	15 mg
	Ulcerative Colitis, Crohn's disease	Induction: 45 mg Maintenance: 15 mg or 30 mg
Stage 4 and above **(GFR below 30 mL/min/1.73 m^2)**	Rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, atopic dermatitis	15 mg
	Ulcerative Colitis, Crohn's disease	Induction: 30 mg Maintenance: 15 mg

Use in Hepatic Impairment

No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. RINVOQ is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) (see **5 PHARMACOLOGICAL PROPERTIES**).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

RINVOQ must not be used in combination with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

4.4 Special warnings and precautions for use

Therapy with RINVOQ should be initiated and monitored by a specialist physician well versed in the use of immunomodulatory therapeutic agents like RINVOQ, with expertise in the management of the indicated conditions.

Mortality

In a large, randomised, post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ (see also subsections on Major Adverse Cardiovascular Events (MACE), Thrombosis, Malignancy, Non-Melanoma Skin Cancer and Use in 65 years of age and older).

Major Adverse Cardiovascular Events (MACE)

Events of MACE were observed in clinical studies of RINVOQ.

In a large, randomised, post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors. MACE, including events of myocardial infarction, were more common in older patients and in patients who were current or past smokers.

In patients 65 years of age and older, patients who are current or past long-time smokers and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, RINVOQ should only be used if no suitable treatment alternatives are available.

Thrombosis

Serious and sometimes fatal events of thrombosis, including deep vein thrombosis (DVT), arterial thrombosis and pulmonary embolism (PE), have occurred in patients treated with JAK inhibitors, including upadacitinib.

In a large, randomised, post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a dose-dependent increased risk for these thrombotic events was observed with tofacitinib–compared to TNF inhibitors (see Section **4.8 Adverse Effects (Undesirable Effects)**).

In patients with cardiovascular or malignancy risk factors (see also subsections on Major Adverse Cardiovascular Events (MACE) and Malignancy), RINVOQ should only be used if no suitable treatment alternatives are available.

Avoid RINVOQ in patients with an increased risk of thrombosis or in whom risk factors are identified. VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormonal therapy, and inherited coagulation disorder. Promptly evaluate patients with signs and symptoms of VTE and discontinue RINVOQ in patients with suspected VTE, regardless of dose or indication.

Patients should be re-evaluated periodically during RINVOQ treatment to assess for changes in VTE risk.

Retinal vein occlusion

Retinal vein occlusion has been reported in patients treated with JAK inhibitors, including upadacitinib. Patients should be advised to promptly seek medical care in case they experience symptoms suggestive of retinal vein occlusion.

Malignancy

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors including RINVOQ. A higher rate of malignancies, driven by non-melanoma skin cancer (NMSC), was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

In a large, randomised, post-marketing safety study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and NMSC, was observed with tofacitinib compared to TNF inhibitors.

In patients 65 years of age and older, patients who are current or past long-time smokers, or patients with other malignancy risk factors (e.g. current malignancy or history of malignancy), RINVOQ should only be use if no suitable treatment alternatives are available.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ (see **Section 4.8 Adverse Effects**). A higher rate of NMSC was observed with RINVOQ 30 mg compared to RINVOQ 15 mg. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Use in patients 65 years of age and older

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised post-marketing study of tofacitinib (another JAK inhibitor), RINVOQ should only be used in these patients if no suitable treatment alternatives are available.

In patients 65 years of age and older, there is an increased risk of adverse reactions with RINVOQ 30 mg once daily. Consequently, the recommended dose for long-term use in this patient population is 15 mg once daily [see **Sections 4.2 Dose and method of administration and 4.8 Adverse effects (Undesirable effects)**].

Of the 4381 patients treated in the five Phase 3 clinical studies, a total of 906 rheumatoid arthritis patients were 65 years of age or older. Of the 1827 patients treated in the two psoriatic arthritis Phase 3 clinical studies, a total of 274 patients were 65 years of age or older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections, in the elderly. There are limited data in patients aged 75 years and older.

Of the 2485 patients treated in the atopic dermatitis Phase 3 clinical studies, 115 were 65 years of age or older. 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.

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, 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 dose once daily group.

Of the 673 patients who responded to RINVOQ 45 mg induction treatment and received maintenance treatment in the Crohn’s disease 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.

Immunosuppressive Medicinal Products

Combination with other potent immunosuppressants such as azathioprine, cyclosporin, tacrolimus, and biologic DMARDs or other JAK inhibitors has not been evaluated in clinical

studies and is not recommended as a risk of additive immunosuppression cannot be excluded (see **4.3 CONTRAINDICATIONS**).

Medication Residue in Stool

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic (e.g. ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Patients should be instructed to contact their healthcare provider if medication residue is observed repeatedly. Patients should be clinically monitored, and alternative treatment should be considered if there is an inadequate therapeutic response.

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 **4.8 ADVERSE EFFECTS**). Cases of bacterial meningitis have been reported in patients receiving upadacitinib. Among opportunistic infections, tuberculosis, multi-dermatomal herpes zoster, oral/oesophageal candidiasis, cryptococcosis, pneumocystosis and eczema herpeticum, were reported with RINVOQ. A higher rate of serious infections was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

Avoid use of RINVOQ in patients with an active, serious infection, including localised 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 travelled 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. RINVOQ may be resumed once the infection is controlled.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients 65 years of age and older, RINVOQ should only be used if no suitable treatment alternatives are available.

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 (see **4.8 ADVERSE EFFECTS**). The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. 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 Phase 3 studies of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Vaccination and Vaccine Studies

No data are available on the response to vaccination with live vaccines in patients receiving RINVOQ. Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ treatment, it is recommended that patients be

brought up to date with all immunisations, including prophylactic zoster vaccinations and COVID-19 vaccinations, in agreement with current immunisation guidelines.

The influence of RINVOQ on the humoral response following administration of herpes zoster (recombinant varicella zoster, RVZ) vaccine was evaluated in 93 patients with rheumatoid arthritis under stable treatment with RINVOQ 15 mg. 98% of patients (n=91) were on concomitant methotrexate. 49% of patients were on oral corticosteroids at baseline. Vaccination resulted in a satisfactory humoral response, defined as ≥ 4-fold increase in pre-vaccination concentration of anti-glycoprotein E titre levels at Week 16 (4 weeks post-dose 2 vaccination), in 88% (95% CI: 81.0, 94.5) of patients treated with RINVOQ 15 mg.

The influence of RINVOQ on the humoral response following the administration of inactivated pneumococcal 13 – valent conjugate vaccine was evaluated in 111 patients with rheumatoid arthritis under stable treatment with RINVOQ 15 mg (N = 87) or 30 mg (N = 24). 97% of patients (N = 108) were on concomitant methotrexate. The primary outcome was the proportion of patients with satisfactory humoral response to inactivated pneumococcal 13-valent conjugate vaccine four weeks post-vaccination. Satisfactory humoral response to inactivated pneumococcal 13-valent conjugate vaccine was defined as ≥ 2-fold increase from baseline in antibody concentration to at least 6 of the 12 pneumococcal antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F). Results at Week 4 demonstrated a satisfactory humoral response in 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with RINVOQ 15 mg and 30 mg respectively.

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 **4.8 ADVERSE EFFECTS**).

Gastrointestinal Perforations

Events of gastrointestinal perforations have been reported in clinical trials (see **4.8 ADVERSE EFFECTS – Specific Adverse Reactions**) and from post-marketing sources. RINVOQ should be used with caution in patients who may be at risk for gastrointestinal perforation (e.g., patients with diverticular disease, a history of diverticulitis, or who are taking nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or opioids). Patients with active Crohn's disease are at increased risk for developing intestinal perforation. Patients presenting with

new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Embryofetal Toxicity

RINVOQ may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception (see **4.6 FERTILITY, PREGNANCY AND LACTATION**).

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of JAK inhibitors, including upadacitinib, in patients receiving treatment for diabetes. Dose adjustment of anti-diabetic medicinal products may be necessary in the event that hypoglycaemia occurs.

Laboratory Tests

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC <1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3) [see **4.2 DOSE AND METHOD OF ADMINISTRATION**].

Lymphopenia

ALCs <500 cells/mm^3 were reported in RINVOQ clinical studies.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3) [see **4.2 DOSE AND METHOD OF ADMINISTRATION**].

Anaemia

Decreases in haemoglobin levels to <8 g/dL were reported in RINVOQ clinical studies.

Evaluate haemoglobin at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low haemoglobin level (i.e., less than 8 g/dL) [see **4.2 DOSE AND METHOD OF ADMINISTRATION**].

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 **4.8 ADVERSE EFFECTS**). 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.

Patients should be monitored 12 weeks after initiation of treatment and thereafter according to the international clinical guidelines for hyperlipidaemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo.

Evaluate at baseline 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 should be interrupted until this diagnosis is excluded.

Use in Hepatic Impairment

See **4.2 DOSE AND METHOD OF ADMINISTRATION** and **5 PHARMACOLOGICAL PROPERTIES**.

Use in Renal Impairment

See **4.2 DOSE AND METHOD OF ADMINISTRATION** and **5 PHARMACOLOGICAL PROPERTIES**.

Paediatric Use

Atopic Dermatitis

The safety and efficacy of RINVOQ in adolescents weighing <40kg and in children aged 0 to less than 12 years have not yet been established. No data are available.

Rheumatoid Arthritis, Psoriatic Arthritis, Non-radiographic Axial Spondyloarthritis, Ankylosing Spondylitis, Ulcerative Colitis, Crohn's Disease

The safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 18 years have not yet been established. No data are available.

Effects on Laboratory Tests

No data suggest that RINVOQ will affect the function of any laboratory test.

4.5 Interactions with other medicines and other forms of interactions

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin and grapefruit). 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 with atopic dermatitis 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 16 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 and the recommended maintenance dose is 15 mg once daily.

Food or drink containing grapefruit should be avoided during treatment with upadacitinib.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampicin and phenytoin), which may lead to reduced therapeutic effect of RINVOQ. Patients should be monitored for changes in disease activity if RINVOQ is co-administered with strong CYP3A4 inducers.

Potential for Other Drugs to Affect the Pharmacokinetics of Upadacitinib

Upadacitinib is metabolised *in vitro* by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 3.

Upadacitinib is a substrate of P-glycoprotein and BCRP. The clinical relevance of this is unknown.

Table 3. Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs

		Ratio (90% CI)[a]	
Co-administered Drug	**Regimen of Co-administered Drug**	**C_{max}**	**AUC**
Methotrexate	10 to 25 mg/week	0.97 (0.86-1.09)	0.99 (0.93-1.06)
Strong CYP3A4 inhibitor: Ketoconazole	400 mg once daily x 6 days	1.70 (1.55-1.89)	1.75 (1.62-1.88)
Strong CYP3A4 inducer: Rifampicin	600 mg once daily x 9 days	0.49 (0.44-0.55)	0.39 (0.37-0.42)
OATP1B inhibitor: Rifampicin	600 mg single dose	1.14 (1.02-1.28)	1.07 (1.01-1.14)

CI: Confidence interval
[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.

Methotrexate, inhibitors of OATP1B transporters, and pH modifying medications (e.g., antacids or proton pump inhibitors) have no effect on upadacitinib plasma exposures. CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics, indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures.

Potential for Upadacitinib to Affect the Pharmacokinetics of Other Drugs

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

Clinical studies indicate that upadacitinib has no clinically relevant effects on the pharmacokinetics of co-administered drugs. Summary of results from clinical studies which

evaluated the effect of upadacitinib on plasma exposures of other drugs is provided in Table 4.

Table 4. Change in Pharmacokinetics of Co-administered Drugs or In Vivo Markers of CYP Activity in the Presence of Upadacitinib

		Ratio (90% CI)[a]	
Co-administered Drug or CYP Activity Marker	**Multiple-Dose Regimen of Upadacitinib**	**C_{max}**	**AUC**
Methotrexate	6 mg to 24 mg twice daily[b]	1.03 (0.86-1.23)	1.14 (0.91-1.43)
Sensitive CYP1A2 Substrate: Caffeine	30 mg once daily[c]	1.13 (1.05-1.22)	1.22 (1.15-1.29)
Sensitive CYP2D6 Substrate: Dextromethorphan	30 mg once daily[c]	1.09 (0.98-1.21)	1.07 (0.95-1.22)
Sensitive CYP2C9 Substrate: S-Warfarin	30 mg once daily[c]	1.07 (1.02-1.11)	1.11 (1.07-1.15)
Sensitive CYP2C19 Marker: 5-OH Omeprazole to Omeprazole metabolic ratio	30 mg once daily[c]	--	1.09 (1.00-1.19)
CYP2B6 Substrate: Buproprion	30 mg once daily[c]	0.87 (0.79-0.96)	0.92 (0.87-0.98)
Sensitive CYP3A Substrate: Midazolam	30 mg once daily[c]	0.74 (0.68-0.80)	0.74 (0.68-0.80)
Sensitive CYP3A Substrate: Midazolam	45 mg once daily[c]	0.75 (0.69-0.83)	0.76 (0.69-0.83)
Dextromethorphan	45 mg once daily[c]	1.30 (1.13-1.50)	1.35 (1.18-1.54)
Rosuvastatin	30 mg once daily[c]	0.77 (0.63-0.94)	0.67 (0.56-0.82)
Atorvastatin	30 mg once daily[c]	0.88 (0.79-0.97)	0.77 (0.70-0.85)
Ethinylestradiol	30 mg once daily[c]	0.96 (0.89-1.02)	1.11 (1.04-1.19)
Levonorgestrel	30 mg once daily[c]	0.96 (0.87-1.06)	0.96 (0.85-1.07)

CYP: cytochrome P450; CI: Confidence interval
[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of medication alone
[b] Immediate-release formulation
[c] Modified-release formulation

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Based on findings in rats, treatment with upadacitinib does not reduce fertility in males or females of reproductive potential.

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study, respectively (approximately 46 and 132 times the clinical dose of 15 mg, approximately 24 and 69 times the clinical dose of 30 mg, and 16 and 45 times the clinical dose of 45 mg on an AUC basis for males and females, respectively).

Use in Pregnancy (Pregnancy Category D)

RINVOQ should not be used during pregnancy. There are limited human data on the use of upadacitinib in pregnant women. 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. Pregnant women should be advised of the potential risk to a fetus.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of RINVOQ.

Upadacitinib crossed the placenta in both rats (significantly) and rabbits (to a lesser degree). Teratogenicity was seen in both species when pregnant animals received upadacitinib during the period of organogenesis. In rats, an increased incidence of skeletal malformations (misshapen humerus, bent scapula and bent bones of the fore- and hind-limbs) and variations (bent ribs) was seen at doses greater than or equal to 4 mg/kg/day. No adverse embryofetal effects were seen at 1.5 mg/kg/day (exposures below the AUC from a clinical dose of 15 mg, 30 mg or 45 mg). In rabbits, an increased incidence of fetal cardiac malformations (dilated aortic arch, discontinuous interventricular septum, constricted or smaller pulmonary trunk, absent pulmonary valve and a larger ventricle) was seen following maternal exposure to 25 mg/kg/day. Embryofetal lethality and abortions were also seen at this dose. Exposures at the no effect level were marginally above the AUC from a clinical dose of 15 mg, approximately the same as the AUC from a clinical dose of 30 mg, and below the AUC from a clinical dose of 45 mg (exposure margin is 0.8 times the exposure at 45 mg).

Use in Lactation

It is unknown whether upadacitinib/metabolites are excreted in human milk. Data in animals have shown excretion of upadacitinib in milk. Following administration of upadacitinib to lactating rats, the concentrations of upadacitinib in milk over time was approximately 30-fold higher exposure in milk relative to maternal plasma. Approximately 97% of drug-related material in milk was parent drug.

A risk to newborns/infants cannot be excluded. RINVOQ should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

RINVOQ may have a minor influence on the ability to drive and use machines because vertigo may occur during treatment with RINVOQ.

4.8 Adverse effects (Undesirable effects)

Adverse Events Reported in Clinical Trials

Rheumatoid Arthritis

A total of 4443 patients with rheumatoid arthritis were treated with upadacitinib in clinical studies representing 5263 patient-years of exposure, of whom 2972 were exposed to upadacitinib for at least one year. In the Phase 3 studies, 2630 patients (2655.1 patient-years of drug exposure) received at least 1 dose of RINVOQ 15 mg, of whom 1607 were exposed for at least one year.

Three placebo-controlled studies were integrated (1035 patients on RINVOQ 15 mg once daily and 1042 patients on placebo) to evaluate the safety of RINVOQ 15 mg in combination with csDMARDs in comparison to placebo for up to 12/14 weeks after treatment initiation. Two methotrexate (MTX)-controlled studies were integrated (534 patients on RINVOQ 15 mg and 530 patients on MTX) to evaluate the safety of RINVOQ 15 mg as monotherapy in comparison to MTX monotherapy for up to 12/14 weeks (see Table 5).

Table 5. Summary of Adverse Events reported by ≥ 1% of rheumatoid arthritis patients treated with RINVOQ (all causalities) – double-blind, placebo controlled, adalimumab (ADA), and MTX controlled up to 12/14 weeks.

Body System/ Adverse Event	Combination Therapy			Monotherapy	
	RINVOQ 15 mg + csDMARDs N=1035 n (%)	Placebo + csDMARDs N=1042 n (%)	ADA + MTX N=327 n (%)	RINVOQ 15 mg N=534 n (%)	MTX N=530 n (%)
Infections and infestations					
Bronchitis	32 (3.1)	21 (2.0)	8 (2.4)	8 (1.5)	11 (2.1)
Gastroenteritis	16 (1.5)	7 (0.7)	0	1 (0.2)	7 (1.3)
Influenza	11 (1.1)	5 (0.5)	2 (0.6)	0	3 (0.6)
Nasopharyngitis	46 (4.4)	33 (3.2)	8 (2.4)	15 (2.8)	13 (2.5)
Pharyngitis	15 (1.4)	8 (0.8)	7 (2.1)	5 (0.9)	4 (0.8)

Body System/ Adverse Event	Combination Therapy			Monotherapy	
	RINVOQ 15 mg + csDMARDs N=1035 n (%)	Placebo + csDMARDs N=1042 n (%)	ADA + MTX N=327 n (%)	RINVOQ 15 mg N=534 n (%)	MTX N=530 n (%)
Sinusitis	15 (1.4)	7 (0.7)	4 (1.2)	6 (1.1)	8 (1.5)
Upper respiratory tract infection	53 (5.1)	38 (3.6)	6 (1.8)	17 (3.2)	23 (4.3)
Urinary tract infection	42 (4.1)	34 (3.3)	13 (4.0)	23 (4.3)	17 (3.2)
Blood and lymphatic system disorders					
Anaemia	10 (1.0)	16 (1.5)	4 (1.2)	5 (0.9)	5 (0.9)
Leukopenia	16 (1.5)	5 (0.5)	2 (0.6)	7 (1.3)	5 (0.9)
Lymphopenia	13 (1.3)	11 (1.1)	2 (0.6)	2 (0.4)	4 (0.8)
Neutropenia	19 (1.8)	2 (0.2)	1 (0.3)	6 (1.1)	2 (0.4)
Metabolism and nutrition disorders					
Hypercholesterolemia	11 (1.1)	2 (0.2)	4 (1.2)	2 (0.4)	0
Nervous system disorders					
Headache	33 (3.2)	38 (3.6)	4 (1.2)	9 (1.7)	7 (1.3)
Dizziness	10 (1.0)	8 (0.8)	5 (1.5)	6 (1.1)	6 (1.1)
Vascular disorders					
Hypertension	24 (2.3)	22 (2.1)	4 (1.2)	9 (1.7)	9 (1.7)
Respiratory, thoracic and mediastinal disorders					
Cough	23 (2.2)	10 (1.0)	4 (1.2)	9 (1.7)	5 (0.9)
Gastrointestinal disorders					
Constipation	11 (1.1)	5 (0.5)	2 (0.6)	5 (0.9)	2 (0.4)
Diarrhoea	30 (2.9)	26 (2.5)	10 (3.1)	8 (1.5)	9 (1.7)
Nausea	36 (3.5)	23 (2.2)	8 (2.4)	17 (3.2)	13 (2.5)
Vomiting	11 (1.1)	7 (0.7)	4 (1.2)	3 (0.6)	2 (0.4)
Musculoskeletal and connective tissue disorders					
Back pain	21 (2.0)	14 (1.3)	4 (1.2)	4 (0.7)	1 (0.2)
Rheumatoid arthritis (worsening)	11 (1.1)	36 (3.5)	5 (1.5)	4 (0.7)	18 (3.4)
General disorders and administration site conditions					
Pyrexia	12 (1.2)	0	1 (0.3)	3 (0.6)	5 (0.9)
Injury, poisoning and procedural complications					
Fall	10 (1.0)	5 (0.5)	2 (0.6)	4 (0.7)	4 (0.8)
Investigations					
Alanine aminotransferase increased	28 (2.7)	27 (2.6)	5 (1.5)	14 (2.6)	7 (1.3)
Aspartate aminotransferase increased	21 (2.0)	21 (2.0)	6 (1.8)	10 (1.9)	6 (1.1)
Blood creatine phosphokinase increased	26 (2.5)	9 (0.9)	1 (0.3)	11 (2.1)	1 (0.2)
Weight increased	10 (1.0)	3 (0.3)	1 (0.3)	2 (0.4)	4 (0.8)

Adverse Drug Reactions

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Very Common: Upper respiratory tract infections (URTI)*

Uncommon: Pneumonia, Herpes zoster, Herpes simplex**, Oral candidiasis

Blood and lymphatic system disorders

Common: Neutropenia

Metabolism and nutrition disorders

Common: Hypercholesterolemia

Uncommon: Hypertriglyceridemia

Respiratory, thoracic and mediastinal disorders

Common: Cough

Gastrointestinal disorders

Common: Nausea

General disorders

Common: Pyrexia

Investigations

Common: Blood creatine phosphokinase (CPK) increased, ALT increased, AST increased, weight increased

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

** Herpes simplex includes: oral herpes

Specific Adverse Reactions

Infections

In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg group was 27.4% compared to 20.9% in the placebo group. In MTX-controlled studies, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group. The overall long-term rate of infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies (2630 patients) was 93.7 events per 100 patient-years.

In placebo-controlled clinical studies with background DMARDs, the frequency of serious infection over 12/14 weeks in the RINVOQ 15 mg group was 1.2% compared to 0.6% in the placebo group. In MTX-controlled studies, the frequency of serious infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 0.6% compared to 0.4% in the MTX group. The overall long-term rate of serious infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most frequently reported serious infections were pneumonia and cellulitis. The rate of serious infections remained stable with long-term exposure.

There was a higher rate of serious infections in patients ≥ 75 years of age, although data are limited.

The frequencies of infection Adverse Drug Reactions (ADRs) for upadacitinib compared to placebo were: URTI (13.5% vs 9.5%), pneumonia (0.5% vs 0.3%), herpes zoster (0.7% vs 0.2%), herpes simplex (0.8% vs 0.5%), and oral candidiasis (0.4% vs <0.1%). Most of the herpes zoster events involved a single dermatome and were non-serious.

Tuberculosis

In placebo-controlled clinical studies with background DMARDs, there were no active cases of TB reported in any treatment group. In MTX-controlled studies, there were no cases over 12/14 weeks in either the RINVOQ 15 mg monotherapy group or the MTX group. The overall long-term rate of active TB for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.1 events per 100 patient-years.

Opportunistic Infections (excluding tuberculosis)

In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the RINVOQ 15 mg group was 0.5% compared to 0.3% in the placebo group. In MTX-controlled studies, there were no cases of opportunistic infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group and 0.2% in the MTX group. The overall long-term rate of opportunistic infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.6 events per 100 patient-years.

Malignancy

In placebo-controlled clinical studies with background DMARDs, the frequency of malignancies excluding NMSC over 12/14 weeks in the RINVOQ 15 mg group was <0.1% compared to <0.1% in the placebo group. In MTX-controlled studies, the frequency of malignancies excluding NMSC over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 0.6% compared to 0.2% in the MTX group. The overall long-term incidence rate of malignancies excluding NMSC for the RINVOQ 15 mg group in the clinical trial program was 0.8 per 100 patient-years.

Gastrointestinal Perforations

In placebo-controlled clinical studies with background DMARDs, the frequency of gastrointestinal perforations in the RINVOQ 15 mg group was 0.2% compared to 0% in the placebo group. In MTX-controlled studies, there were no gastrointestinal perforations over 12/14 weeks in either the RINVOQ 15 mg monotherapy group or the MTX group. The overall long-term rate of gastrointestinal perforation for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.08 events per 100 patient-years.

Thrombosis

In placebo-controlled studies with background DMARDs, there were two (0.2%) venous thrombosis events (pulmonary embolism or deep vein thrombosis) in the RINVOQ 15 mg group compared to one event (0.1%) in the placebo group. In MTX-controlled studies, there was one venous thrombosis event (0.2%) over 12/14 weeks in the RINVOQ 15 mg monotherapy group and there were no events in the MTX group. The overall long-term incidence rate of venous thrombosis events for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.6 per 100 patient-years.

Hepatic transaminase elevations

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, compared to 1.5% and 0.7%, respectively, of patients treated with placebo. Most cases of hepatic transaminase elevations were asymptomatic and transient.

In MTX-controlled studies, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15mg, compared to 1.9% and 0.9%, respectively, of patients treated with MTX.

The pattern and incidence of elevation in ALT/AST remained stable over time including in long-term extension studies.

Lipid elevations

Upadacitinib 15mg treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol. There was no change in the LDL/HDL ratio. Elevations were observed at 2 to 4 weeks of treatment and remained stable with longer-term treatment. Among patients in controlled studies with baseline values below the specified limits, the following frequencies of patients were observed to shift above the specified limits on at least one occasion during 12/14 weeks (including patients who had an isolated elevated value):

- Total cholesterol ≥ 5.17 mmol/L (200 mg/dL): 62% vs. 31%, in the upadacitinib 15 mg and placebo groups, respectively
- LDL cholesterol ≥ 3.36 mmol/L (130 mg/dL): 42% vs. 19%, in the upadacitinib 15 mg and placebo groups, respectively
- HDL cholesterol ≥ 1.03 mmol/L (40 mg/dL): 89% vs. 61%, in the upadacitinib 15 mg and placebo groups, respectively
- Triglycerides ≥ 2.26 mmol/L (200 mg/dL): 25% vs. 15%, in the upadacitinib 15 mg and placebo groups, respectively

Creatine phosphokinase elevations

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo

groups, respectively. Most elevations > 5 x ULN were transient and did not require treatment discontinuation. Mean CPK values increased by 4 weeks with a mean increase of 60 U/L at 12 weeks and then remained stable at an increased value thereafter including with extended therapy.

Neutropenia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ANC <1000 cells/mm^3. The pattern and incidence of decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

Lymphopenia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively.

Anaemia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, haemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups.

Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical studies representing 1639.2 patient-years of exposure, 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).

Non-radiographic Axial Spondyloarthritis

A total of 286 patients with non-radiographic axial spondyloarthritis were treated with RINVOQ 15 mg in the clinical study representing 269.4 patient-years of exposure, of whom 134 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. No new safety findings were identified.

Ankylosing Spondylitis

A total of 596 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the two clinical studies representing 843 patient-years of exposure, of whom 490 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. No new safety findings were identified.

Atopic Dermatitis

A total of 2893 patients with atopic dermatitis were treated with upadacitinib in clinical studies representing approximately 2096 patient-years of exposure, of whom 614 were exposed for at least one year. In the three global Phase 3 studies, 1238 patients received at least 1 dose of RINVOQ 15 mg, of whom 246 were exposed for at least one year and 1242 patients received at least 1 dose of RINVOQ 30 mg, of whom 263 were exposed for at least one year.

Four global placebo-controlled studies (one Phase 2 study and three Phase 3 studies) were integrated (899 patients on RINVOQ 15 mg once daily, 906 patients on RINVOQ 30 mg once daily and 902 patients on placebo) to evaluate the safety of RINVOQ 15 mg and 30 mg in comparison to placebo for up to 16 weeks after treatment initiation (see Table 6).

Table 6. Adverse Events Reported in ≥1% of Atopic Dermatitis Patients Treated with RINVOQ 15 mg or 30 mg in Placebo-Controlled Studies

Body System / Adverse Event	RINVOQ 15 mg QD (N=899) n (%)	RINVOQ 30 mg QD (N=906) n (%)	Placebo (N=902) n (%)
All adverse events	574 (63.8)	630 (69.5)	528 (58.5)
Infections and infestations			
Folliculitis	19 (2.1)	29 (3.2)	10 (1.1)
Gastroenteritis	9 (1.0)	12 (1.3)	13 (1.4)
Herpes simplex	15 (1.7)	21 (2.3)	5 (0.6)
Herpes zoster	14 (1.6)	14 (1.5)	5 (0.6)
Impetigo	9 (1.0)	9 (1.0)	10 (1.1)
Influenza	19 (2.1)	14 (1.5)	3 (0.3)
Nasopharyngitis	79 (8.8)	94 (10.4)	64 (7.1)
Oral herpes	23 (2.6)	47 (5.2)	9 (1.0)
Pharyngitis	10 (1.1)	7 (0.8)	2 (0.2)
Upper respiratory tract infection	70 (7.8)	83 (9.2)	58 (6.4)
Urinary tract infection	12 (1.3)	22 (2.4)	18 (2.0)
Viral upper respiratory tract infection	12 (1.3)	11 (1.2)	6 (0.7)
Blood and lymphatic system disorders			
Anaemia	2 (0.2)	9 (1.0)	2 (0.2)
Neutropenia	7 (0.8)	21 (2.3)	2 (0.2)
Nervous system disorder			
Dizziness	10 (1.1)	11 (1.2)	3 (0.3)
Headache	50 (5.6)	57 (6.3)	39 (4.3)
Vascular disorders			
Hypertension	6 (0.7)	11 (1.2)	8 (0.9)
Respiratory, thoracis and mediastinal disorders			
Asthma	11 (1.2)	6 (0.7)	13 (1.4)
Cough	29 (3.2)	27 (3.0)	13 (1.4)
Oropharyngeal pain	19 (2.1)	20 (2.2)	9 (1.0)
Gastrointestinal disorders			
Abdominal pain	10 (1.1)	10 (1.1)	4 (0.4)
Abdominal pain upper	16 (1.8)	11 (1.2)	3 (0.3)
Diarrhoea	31 (3.4)	29 (3.2)	23 (2.5)
Dyspepsia	9 (1.0)	9 (1.0)	1 (0.1)
Nausea	24 (2.7)	24 (2.6)	5 (0.6)
Vomiting	6 (0.7))	11 (1.2)	6 (0.7)
Skin and subcutaneous tissue disorders			
Acne	86 (9.6)	137 (15.1)	20 (2.2)
Dermatitis acneiform	5 (0.6)	11 (1.2)	0
Dermatitis atopic	31 (3.4)	14 (1.5)	74 (8.2)
Urticaria	8 (0.9)	14 (1.5)	3 (0.3)
Musculoskeletal and connective tissue disorders			
Arthralgia	10 (1.1)	11 (1.2)	7 (0.8)
Back pain	9 (1.0)	10 (1.1)	12 (1.3)

Body System / Adverse Event	RINVOQ 15 mg QD (N=899) n (%)	RINVOQ 30 mg QD (N=906) n (%)	Placebo (N=902) n (%)
Myalgia	9 (1.0)	16 (1.8)	7 (0.8)
General disorders and administration site conditions			
Fatigue	12 (1.3)	17 (1.9)	5 (0.6)
Influenza like illness	13 (1.4)	17 (1.9)	8 (0.9)
Pyrexia	15 (1.7)	19 (2.1)	9 (1.0)
Investigations			
Blood creatine phosphokinase increased	41 (4.6)	50 (5.5)	21 (2.3)
Weight increased	16 (1.8)	17 (1.9)	5 (0.6)

The adverse reactions listed below are uncommon (≥ 1/1,000 to < 1/100). Within each grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and Infestations

Uncommon: Pneumonia, oral candidiasis

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: Non-melanoma skin cancer***

Metabolism and nutrition disorders

Uncommon: Hypercholesterolemia, hypertriglyceridemia

Investigations

Uncommon: ALT increased; AST increased

*** Presented as a grouped term

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

Specific Adverse Reactions

Infections

In placebo-controlled clinical studies, the frequency of infection over 16 weeks in the RINVOQ 15 mg and 30 mg groups was 39% and 43% respectively, compared to 30% in the placebo group. The long-term rate of infections for the RINVOQ 15 mg and 30 mg groups was 123.7 and 139.1 events per 100 patient-years, respectively.

In placebo-controlled clinical studies, the frequency of serious infection over 16 weeks in the RINVOQ 15 mg and 30 mg groups were 0.8% and 0.4% respectively, compared to 0.6% in the placebo group. The long-term rate of serious infections for the RINVOQ 15 mg and 30 mg groups was 2.4 and 3.4 events per 100 patient-years, respectively. The most frequently reported serious infection was pneumonia.

Tuberculosis

In placebo-controlled clinical studies over 16 weeks, there were no active cases of tuberculosis reported in any treatment group. The overall long-term rate of tuberculosis for both the RINVOQ 15 mg and 30 mg groups was 0.1 events per 100 patient-years.

Opportunistic Infections (excluding tuberculosis)

All opportunistic infections (excluding tuberculosis and herpes zoster) reported in the global atopic dermatitis studies were eczema herpeticum. In placebo-controlled clinical studies, the frequency of eczema herpeticum over 16 weeks in the RINVOQ 15 mg and 30 mg groups was 0.7% and 0.8% respectively, compared to 0.4% in the placebo group. The long-term rate of eczema herpeticum for the RINVOQ 15 mg and 30 mg groups was 2.1 and 2.2 events per 100 patient-years, respectively.

The long-term rate of herpes zoster for the RINVOQ 15 mg and 30 mg groups was 3.8 and 5.3 events per 100 patient-years, respectively. Most of the herpes zoster events involved a single dermatome and were non-serious.

Malignancy

In placebo-controlled clinical studies, the frequency of malignancies excluding NMSC over 16 weeks in the RINVOQ 15 mg and 30 mg groups was 0% and 0.4% respectively, compared to 0% in the placebo group. The long-term incidence rate of malignancies excluding NMSC for the RINVOQ 15 mg and 30 mg groups was 0 and 0.7 per 100 patient years, respectively.

Gastrointestinal Perforations

There were no cases of gastrointestinal perforations reported in any treatment group.

Thrombosis

In placebo-controlled studies over 16 weeks, there were no venous thrombosis events (pulmonary embolism or deep vein thrombosis) in the RINVOQ 15 mg and 30 mg groups

compared to 1 event (0.1%) in the placebo group. The long-term incidence rate of venous thrombosis for RINVOQ treatment across the atopic dermatitis clinical studies was <0.1 per 100 patient-years.

Hepatic transaminase elevations

In placebo-controlled studies, for up to 16 weeks, alanine transaminase (ALT) ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 0.7%, 1.4% and 1.1% of patients treated with RINVOQ 15 mg, 30 mg and placebo, respectively. In these trials, aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 1.2%, 1.1% and 0.9% of patients treated with RINVOQ 15mg, 30 mg and placebo, respectively. Most cases of hepatic transaminase elevations were asymptomatic and transient. The pattern and incidence of elevation in ALT/AST remained stable over time including in long-term extension studies.

Lipid elevations

RINVOQ 15 mg and 30 mg treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, LDL cholesterol and HDL cholesterol. Among patients in the controlled studies with baseline values below the specified limits, the following frequencies of patients were observed to shift to above the specified limits on at least one occasion during 16 weeks (including patients who had an isolated elevated value):

- Total cholesterol ≥ 5.17 mmol/L (200 mg/dL): 43.0%, 49.1% and 24.7% in the upadacitinib 15 mg, 30 mg, and placebo groups, respectively
- LDL cholesterol ≥ 3.36 mmol/L (130 mg/dL): 28.1%, 31.6% and 18.9% in the upadacitinib 15 mg, 30 mg, and placebo groups, respectively
- HDL cholesterol ≥ 1.03 mmol/L (40 mg/dL): 90.7%, 93.1% and 69.7% in the upadacitinib 15 mg, 30 mg, and placebo groups, respectively
- Triglycerides ≥ 2.26 mmol/L (200 mg/dL): 19.2%, 19.7% and 17.7% in the upadacitinib 15 mg, 30 mg, and placebo groups, respectively

Small increases in LDL cholesterol were observed after Week 16.

Creatine phosphokinase elevations

In placebo-controlled studies, for up to 16 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 3.3%, 4.4% and 1.7% of patients over 16 weeks in the RINVOQ 15 mg, 30 mg and placebo

groups, respectively. Most elevations > 5 x ULN were transient and did not require treatment discontinuation.

Neutropenia

In placebo-controlled studies, for up to 16 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 0.4%, 1.3% and 0% of patients in the RINVOQ 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ANC <1000 cells/mm^3. The pattern and incidence of decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

Lymphopenia

In placebo-controlled studies, for up to 16 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.1%, 0.3% and 0.1% of patients in the RINVOQ 15 mg, 30 mg and placebo groups, respectively.

Anaemia

In placebo-controlled studies, haemoglobin decreases below 8 g/dL in at least one measurement occurred in 0%, 0.1% and 0% of patients in the RINVOQ 15 mg, 30 mg and placebo groups, respectively.

Paediatric population

A total of 541 adolescents aged 12 to 17 years weighing at least 40 kg with atopic dermatitis were treated in the global Phase 3 studies (n=343) and the supplemental adolescent substudies. The safety profile for RINVOQ 15 mg was similar in adolescents and adults. With long-term exposure, the adverse drug reaction of skin papilloma was identified and reported in 3.4% of adolescents with atopic dermatitis treated with RINVOQ 15 mg.

Ulcerative Colitis

RINVOQ has been studied in patients with moderately to severely active UC in one Phase 2b and three Phase 3 (UC-1, UC-2 and UC-3) randomised, double-blind, placebo-controlled clinical studies and a long-term extension study (see **Section 5: PHARMACOLOGICAL PROPERTIES: Ulcerative Colitis**) with a total of 1313 patients representing 3537 patient-years of exposure, of whom a total of 959 patients were exposed 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 for 8 weeks and 127 subjects were exposed for up to 16 weeks (Table 7).

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 193 were exposed for at least one year and 291 patients received at least one dose of RINVOQ 30 mg, of whom 214 were exposed for at least one year (Table 8).

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

Table 7. Summary of Adverse Events reported by ≥ 1% of ulcerative colitis patients treated with RINVOQ (all causalities) – double-blind, placebo-controlled induction study up to 8 weeks

Body System/ Adverse Event	RINVOQ 45 mg N=719 n (%)	Placebo N=378 n (%)
Infections and Infestations		
Folliculitis	16 (2.2)	2 (0.5)
Nasopharyngitis	31 (4.3)	13 (3.4)
Oral herpes	9 (1.3)	1 (0.3)
Upper respiratory tract infection	16 (2.2)	7 (1.9)
Urinary tract infection	7 (1.0)	7 (1.9)
Blood and lymphatic system disorders		
Anaemia	22 (3.1)	16 (4.2)
Lymphopenia	11 (1.5)	2 (0.5)
Neutropenia	13 (1.8)	1 (0.3)
Nervous system disorder		
Headache	26 (3.6)	18 (4.8)
Vascular disorders		
Hypertension	7 (1.0)	3 (0.8)
Respiratory, thoracic and mediastinal disorders		
Cough	8 (1.1)	5 (1.3)
Oropharyngeal pain	7 (1.0)	2 (0.5)
Gastrointestinal disorders		
Abdominal pain	11 (1.5)	3 (0.8)
Colitis ulcerative	13 (1.8)	35 (9.3)
Constipation	11 (1.5)	3 (0.8)
Haemorrhoids	9 (1.3)	2 (0.5)
Nausea	7 (1.0)	9 (2.4)
Musculoskeletal and connective tissue disorders		
Arthralgia	10 (1.4)	11 (2.9)
Skin and subcutaneous tissue disorders		
Acne	40 (5.6)	4 (1.1)
Rash	17 (2.4)	2 (0.5)

Body System/ Adverse Event	RINVOQ 45 mg N=719 n (%)	Placebo N=378 n (%)
General disorders		
Fatigue	9 (1.3)	5 (1.3)
Pyrexia	18 (2.5)	6 (1.6)
Investigations		
Alanine aminotransferase increased	7 (1.0)	4 (1.1)
Aspartate aminotransferase increased	13 (1.8)	5 (1.3)
Blood creatine phosphokinase increased	37 (5.1)	5 (1.3)
Neutrophil count increased	20 (2.8)	0
White blood cell count decreased	12 (1.7)	1 (0.3)

Maintenance Study (UC-3)

Table 8. Summary of Adverse Events reported by ≥ 2% of ulcerative colitis patients treated with RINVOQ (all causalities) – double-blind, placebo-controlled maintenance study up to 52 weeks

Body System/Adverse Events	RINVOQ 30 mg N=251 n (%)	RINVOQ 15 mg N=250 n (%)	Placebo N=245 n (%)
Infections and infestations			
Bronchitis	2 (0.8)	5 (2.0)	3 (1.2)
COVID-19	10 (4.0)	5 (2.0)	8 (3.3)
Folliculitis	9 (3.6)	5 (2.0)	4 (1.6)
Gastroenteritis	3 (1.2)	5 (2.0)	4 (1.6)
Herpes zoster	14 (5.6)	11 (4.4)	0
Influenza	8 (3.2)	7 (2.8)	3 (1.2)
Nasopharyngitis	26 (10.4)	23 (9.2)	20 (8.2)
Oral herpes	7 (2.8)	5 (2.0)	3 (1.2)
Upper respiratory tract infection	11 (4.4)	12 (4.8)	8 (3.3)
Urinary tract infection	3 (1.2)	7 (2.8)	6 (2.4)
Blood and lymphatic system disorders			
Anaemia	8 (3.2)	9(3.6)	10 (4.1)
Leukopenia	1 (0.4)	5 (2.0)	3 (1.2)
Neutropenia	6 (2.4)	4 (1.6)	3 (1.2)
Nervous system disorders			
Headache	9 (3.6)	8 (3.2)	11 (4.5)
Vascular disorders			
Hypertension	6(2.4)	6 (2.4)	2 (0.8)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	6 (2.4)	3 (1.2)	5 (2.0)
Gastrointestinal disorders			
Abdominal distension	5 (2.0)	2 (0.8)	1 (0.4)
Abdominal pain	4 (1.6)	6 (2.4)	6 (2.4)
Colitis ulcerative	21 (8.4)	31(12.4)	74 (30.2)

Body System/Adverse Events	RINVOQ 30 mg N=251 n (%)	RINVOQ 15 mg N=250 n (%)	Placebo N=245 n (%)
Constipation	6 (2.4)	3 (1.2)	2 (0.8)
Nausea	5 (2.0)	4 (1.6)	5 (2.0)
Musculoskeletal and connective tissue disorders			
Arthralgia	8 (3.2)	15 (6.0)	28 (11.4)
Back pain	1 (0.4)	7 (2.8)	10 (4.1)
Psychiatric disorders			
Insomnia	8 (3.2)	2 (0.8)	7 (2.9)
Skin and subcutaneous tissue disorders			
Acne	9 (3.6)	7 (2.8)	8 (3.3)
Eczema	5 (2.0)	2 (0.8)	5 (2.0)
Rash	11 (4.4)	8(3.2)	9 (3.7)
Urticaria	5 (2.0)	0	2 (0.8)
General disorders and administration site conditions			
Pyrexia	15 (6.0)	8(3.2)	7 (2.9)
Investigations			
Alanine aminotransferase increased	7 (2.8)	7 (2.8)	1 (0.4)
Aspartate aminotransferase increased	5 (2.0)	9 (3.6)	2 (0.8)
Blood cholesterol increased	6 (2.4)	2 (0.8)	0
Blood creatine phosphokinase increased	19 (7.6)	15 (6.0)	5 (2.0)
Gamma-glutamyltransferase increased	1 (0.4)	5 (2.0)	1 (0.4)
Low density lipoprotein increased	5 (2.0)	1 (0.4)	0
Lymphocyte count decreased	4 (1.6)	5 (2.0)	2 (0.8)
Neutrophil count decreased	8 (3.2)	5 (2.0)	2 (0.8)
White blood cell count decreased	6 (2.4)	5 (2.0)	2 (0.8)

Adverse Drug Reactions

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Very Common: Upper respiratory tract infections (URTI)*

Common: Herpes zoster*, Folliculitis, Influenza, Herpes simplex*

Uncommon: Pneumonia*

Blood and lymphatic system disorders
Common: Neutropenia*, Lymphopenia*

Metabolism and nutrition disorders
Common: Hypercholesterolemia*, Hyperlipidemia*

Skin and subcutaneous tissue disorders
Common: Acne*, Rash*

General disorders
Common: Pyrexia

Investigations
Common: Blood creatine phosphokinase (CPK) increased, ALT increased, AST increased
* Presented as grouped term

The safety profile of RINVOQ with long-term treatment was consistent with that in the placebo-controlled period.

Specific Adverse Reactions

Infections

In the placebo-controlled induction studies, the frequency of infection over 8 weeks in the RINVOQ 45 mg group and the placebo group was 20.7% and 17.5%, respectively. In the placebo-controlled maintenance study, the frequency of infection over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 40.4% and 44.2%, respectively, and 38.8% in the placebo group. The long-term rate of infection for RINVOQ 15 mg and 30 mg was 64.5 and 77.8 events per 100 patient-years, respectively.

Serious Infections

In the placebo-controlled induction studies, the frequency of serious infection over 8 weeks in the RINVOQ 45 mg group and the placebo group was 1.3% and 1.3%, respectively. No additional serious infections were observed over 8-week extended induction treatment with RINVOQ 45 mg. In the placebo-controlled maintenance study, the frequency of serious infection over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 3.6%, and 3.2%, respectively, and 3.3% in the placebo group. The long-term rate of serious infection for the

RINVOQ 15 mg and 30 mg groups was 3.0 and 4.6 events per 100 patient-years, respectively. The most frequently reported serious infection in the ulcerative colitis studies was COVID-19 pneumonia.

Tuberculosis

In the clinical studies for ulcerative colitis, there was 1 case of active tuberculosis reported in a patient receiving RINVOQ 15 mg during the long-term extension study.

Opportunistic Infections (excluding tuberculosis)

In the placebo-controlled induction studies over 8 weeks, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) in the RINVOQ 45 mg group was 0.4% and 0.3% in the placebo group. No additional opportunistic infections (excluding tuberculosis and herpes zoster) were observed over the 8-week extended induction treatment with RINVOQ 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) was 0.8% on placebo and in the RINVOQ 15 mg and 30 mg groups. The long-term rate of opportunistic infection (excluding tuberculosis and herpes zoster) for the RINVOQ 15 mg and 30 mg groups was 0.3 and 0.6 events per 100 patient-years, respectively.

In the placebo-controlled induction studies over 8 weeks, the frequency of herpes zoster in the RINVOQ 45 mg group was 0.6% and 0% in the placebo group. The frequency of herpes zoster was 3.9% over 16-week treatment with RINVOQ 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of herpes zoster in the RINVOQ 15 mg and 30 mg groups was 4.4% and 4.0%, respectively, compared to 0% in the placebo group. The long-term rate of herpes zoster for the RINVOQ 15 mg and 30 mg groups was 4.5 and 7.2 events per 100 patient-years, respectively.

Malignancy

In the placebo-controlled induction studies, there were no reports of malignancy. In the placebo-controlled maintenance study, the frequency of malignancies excluding non-melanoma skin cancer (NMSC) in the RINVOQ 15 mg and 30 mg groups was 0.4% and 0.8%, respectively, and 0.4% in the placebo group. The long-term incidence rate of malignancies excluding NMSC for the RINVOQ 15 mg and 30 mg groups was was 0.7 and 0.4 per 100 patient years, respectively.

Gastrointestinal Perforations

In the placebo-controlled maintenance period, gastrointestinal perforation was reported in 1 patient treated with placebo (1.5 per 100 patient-years) and no patients treated with RINVOQ 15 mg or 30 mg. In the long-term extension study, 1 patient treated with RINVOQ 15 mg (0.1 per 100 patient-years) and 1 patient treated with RINVOQ 30 mg (<0.1 per 100 patient-years) reported such events.

Thrombosis

In the placebo-controlled induction studies, the frequency of venous thrombosis (pulmonary embolism or deep vein thrombosis) over 8 weeks in the RINVOQ 45 mg group was 0.1% and 0.3% in the placebo group, respectively. No additional events of venous thrombosis were reported with RINVOQ 45 mg extended induction treatment. In the placebo-controlled maintenance study, the frequency of venous thrombosis over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 0.8% and 0.8%, respectively, and 0% in the placebo group. The long-term incidence rate of venous thrombosis for RINVOQ 15 mg and 30 mg was 0.7 and 0.6 per 100 patient-years, respectively.

Hepatic transaminase elevations

In the placebo-controlled induction studies over 8 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 1.5% and 1.5% of patients treated with RINVOQ 45 mg and 0% and 0.3% with placebo, respectively. In the placebo-controlled maintenance study over 52 weeks, ALT elevations ≥ 3 x ULN in at least one measurement were observed in 2.0% and 4.4% of patients treated with RINVOQ 15 mg and 30 mg and 1.2% with placebo, respectively. AST elevations ≥ 3 x ULN in at least one measurement were observed in 1.6% and 2.0% of patients treated with RINVOQ 15 mg and 30 mg and 0.4% with placebo, respectively. Most cases of hepatic transaminase elevations were asymptomatic and transient. The pattern and incidence of ALT/AST elevations remained generally stable over time including in long-term extension studies.

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 summarised below:

- Total cholesterol ≥ 5.17 mmol/L (200 mg/dL): 49% vs. 11%, in the RINVOQ 45 mg and placebo groups, respectively
- LDL cholesterol ≥ 3.36 mmol/L (130 mg/dL): 27% vs. 9%, in the RINVOQ 45 mg and placebo groups, respectively
- HDL cholesterol ≥ 1.03 mmol/L (40 mg/dL): 79% vs. 36%, in the RINVOQ 45 mg and placebo groups, respectively
- Triglycerides ≥ 2.26 mmol/L (200 mg/dL): 6% vs 4% in the RINVOQ 45 mg and placebo groups, respectively

Creatine phosphokinase elevations

In the placebo-controlled induction studies over 8 weeks, increases in creatine phosphokinase (CPK) values were observed. CPK elevations >5 x ULN were reported in 2.2% and 0.3% of patients in the RINVOQ 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study over 52 weeks, CPK elevations >5 x ULN were reported in 4.4% and 6.8% of patients in the RINVOQ 15 mg and 30 mg groups and 1.2% in the placebo group, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation.

Neutropenia

In the placebo-controlled induction studies over 8 weeks, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 2.8% of patients in the RINVOQ 45 mg group and 0% in the placebo group, respectively. In the placebo-controlled maintenance study over 52 weeks, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.8% and 2.4% of patients in the RINVOQ 15 mg and 30 mg groups and 0.8% in the placebo group, respectively.

Lymphopenia

In the placebo-controlled induction studies over 8 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 2.0% of patients in the RINVOQ 45 mg group and 1.2% in the placebo group. In the placebo-controlled maintenance study over 52 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one

measurement occurred in 1.6% and 0.8% of patients in the RINVOQ 15 mg and 30 mg groups and to 0.8% in the placebo group, respectively.

Anaemia

In the placebo-controlled induction studies over 8 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in 0.3% of patients in the RINVOQ 45 mg group and 2.1% in the placebo group. In the placebo-controlled maintenance study over 52 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in 0.4% and 0.4% of patients in the RINVOQ 15 mg and 30 mg groups and 1.2% in the placebo group, respectively.

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) randomised, double-blind, placebo-controlled clinical studies (*see* **CLINICAL STUDIES**) with a total of 833 patients included in two induction studies and in the maintenance/ long term extension study (LTE) representing 1203 patient-years of exposure, of whom a total of 536 patients were exposed for at least one year starting with the dose of induction treatment.

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 were re-randomised and received at least one dose of RINVOQ 15 mg, of whom 89 were exposed for at least one year and 229 patients were re-randomised and received at least one dose of RINVOQ 30 mg, of whom 107 were exposed for at least one year starting with the first dose of maintenance treatment.

Overall, the safety profile observed in patients with CD treated with RINVOQ was consistent with the known safety profile of RINVOQ.

Table 9. Summary of Adverse Events reported by ≥ 1% of Crohn's disease patients treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (CD-1 and CD-2)

Body System/ Adverse Event	RINVOQ 45 mg N=674 n (%)	Placebo N=347 n (%)
Infections and Infestations		
Folliculitis	9 (1.3)	1 (0.3)
Herpes zoster	15 (2.2)	0
Influenza	20 (3.0)	2 (0.6)
Nasopharyngitis	39 (5.8)	11 (3.2)
Oral herpes	10 (1.5)	4 (1.2)
Upper respiratory tract infection	29 (4.3)	9 (2.6)
Urinary tract infection	13 (1.9)	5 (1.4)
Blood and lymphatic system disorders		
Anaemia	38 (5.6)	18 (5.2)
Iron deficiency anaemia	7 (1.0)	1 (0.3)
Leukopenia	8 (1.2)	1 (0.3)
Neutropenia	8 (1.2)	1 (0.3)
Nervous system disorders		
Dizziness	8 (1.2)	3 (0.9)
Headache	35 (5.2)	16 (4.6)
Paraesthesia	9 (1.3)	3 (0.9)
Respiratory, thoracic and mediastinal disorders		
Cough	14 (2.1)	6 (1.7)
Oropharyngeal pain	11 (1.6)	5 (1.4)
Gastrointestinal disorders		
Abdominal distension	12 (1.8)	7 (2.0)
Abdominal pain	23 (3.4)	17 (4.9)
Abdominal pain upper	8 (1.2)	3 (0.9)
Aphthous ulcer	8 (1.2)	4 (1.2)
Constipation	17 (2.5)	5 (1.4)
Crohn's disease	33 (4.9)	41 (11.8)
Diarrhoea	10 (1.5)	11 (3.2)
Flatulence	10 (1.5)	3 (0.9)
Mouth ulceration	8 (1.2)	3 (0.9)

Body System/ Adverse Event	RINVOQ 45 mg N=674 n (%)	Placebo N=347 n (%)
Nausea	30 (4.5)	16 (4.6)
Vomiting	13 (1.9)	9 (2.6)
Skin and subcutaneous tissue disorders		
Acne	39 (5.8)	5 (1.4)
Rash	15 (2.2)	10 (2.9)
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (2.4)	19 (5.5)
Back pain	11 (1.6)	14 (4.0)
Muscle spasms	9 (1.3)	1 (0.3)
General disorders		
Fatigue	16 (2.4)	10 (2.9)
Pyrexia	28 (4.2)	9 (2.6)
Investigations		
Blood creatine phosphokinase increased	20 (3.0)	4 (1.2)
Lymphocyte count decreased	7 (1.0)	6 (1.7)
White blood cell count decreased	8 (1.2)	1 (0.3)
Hepatobiliary disorders		
Hepatic function abnormal	7 (1.0)	0
Psychiatric disorders		
Anxiety	7 (1.0)	3 (0.9)
Depression	9 (1.3)	1 (0.3)
Insomnia	9 (1.3)	2 (0.6)

Maintenance Study (CD-3)

Table 10. Summary of Exposure-Adjusted Event Rates per 100 Patient Years with ≥ 3 E/100 PYs in Crohn's disease patients treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (CD-3)

Body System/Adverse Events	RINVOQ 15 mg N=221 (PYs=261.3) Events (E/100 PYs)	RINVOQ 30 mg N=229 (PYs=225.3) Events (E/100 PYs)	Placebo N=223 (PYs=138.3) Events (E/100 PYs)
Infections and infestations			
Anal abscess	9 (4)	4 (1.5)	2 (1.4)
Bronchitis	4 (1.8)	9 (3.4)	0
COVID-19	21 (9.3)	31 (11.9)	10 (7.2)
Herpes zoster	8 (3.6)	14 (5.4)	4 (2.9)
Nasopharyngitis	19 (8.4)	10 (3.8)	11 (8)
Pneumonia	7 (3.1)	2 (0.8)	1 (0.7)
Upper respiratory tract infection	10 (4.4)	23 (8.8)	9 (6.5)
Urinary tract infection	13 (5.8)	9 (3.4)	7 (5.1)
Blood and lymphatic system disorders			
Anaemia	10 (4.4)	12 (4.6)	14 (10.1)
Nervous system disorders			
Headache	7 (3.1)	19 (7.3)	4 (2.9)
Respiratory, thoracic and mediastinal disorders			
Cough	8 (3.6)	5 (1.9)	4 (2.9)
Gastrointestinal disorders			
Abdominal pain	14 (6.2)	13 (5)	11 (8)
Constipation	8 (3.6)	4 (1.5)	6 (4.3)
Crohn's disease	50 (22.2)	23 (8.8)	65 (47)
Diarrhoea	12 (5.3)	9 (3.4)	9 (6.5)
Haematochezia	7 (3.1)	5 (1.9)	1 (0.7)
Nausea	10 (4.4)	12 (4.6)	14 (10.1)
Skin and subcutaneous tissue disorders			
Acne	4 (1.8)	12 (4.6)	7 (5.1)
Rash	6 (2.7)	9 (3.4)	12 (8.7)

Body System/Adverse Events	RINVOQ 15 mg N=221 (PYs=261.3) Events (E/100 PYs)	RINVOQ 30 mg N=229 (PYs=225.3) Events (E/100 PYs)	Placebo N=223 (PYs=138.3) Events (E/100 PYs)
Musculoskeletal and connective tissue disorders			
Arthralgia	11 (4.9)	17 (6.5)	15 (10.8)
General disorders and administration site conditions			
Fatigue	12 (5.3)	11 (4.2)	5 (3.6)
Injection site pain	7 (3.1)	5 (1.9)	0
Pyrexia	16 (7.1)	21 (8)	6 (4.3)
Investigations			
Alanine aminotransferase increased	9 (4)	9 (3.4)	0
Aspartate aminotransferase increased	8 (3.6)	12 (4.6)	1 (0.7)
Blood creatine phosphokinase increased	9 (4)	10 (3.8)	4 (2.9)
Lymphocyte count decreased	6 (2.7)	20 (7.7)	5 (3.6)
Neutrophil count decreased	7 (3.1)	4 (1.5)	1 (0.7)
White blood cell count decreased	10 (4.4)	6 (2.3)	1 (0.7)
Table 10 includes safety data from the ongoing long term extension study M14-430 Sub-study 2 for patients remaining on the same dose as in 52-week maintenance period.			

Adverse Drug Reactions

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Very Common: Upper respiratory tract infections (URTI)*

Common: Bronchitis*, Herpes zoster*, Folliculitis, Influenza, Herpes simplex*, Pneumonia*

Uncommon: Oral candidiasis

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Non-melanoma skin cancer*

Blood and lymphatic system disorders
Common: Neutropenia*, Anaemia*

Metabolism and nutrition disorders
Common: Hypercholesterolemia*, Hyperlipidemia*

Skin and subcutaneous tissue disorders
Common: Acne*

General disorders
Common: Pyrexia, Fatigue

Investigations
Common: Blood creatine phosphokinase (CPK) increased, ALT increased, AST increased

Nervous system disorders
Common: Headache*

* Presented as grouped term

Specific Adverse Reactions

Serious infections

In the placebo-controlled induction studies, the frequency of serious infection over 12 weeks in the upadacitinib 45 mg group and the placebo group was 1.9% and 1.7%, respectively. In the placebo-controlled maintenance period, the frequency of serious infection over 52 weeks in the upadacitinib 15 mg and 30 mg groups was 3.2% and 5.7%, respectively, compared to 4.5% in the placebo group. The long-term rate of serious infections for the upadacitinib 15 mg and 30 mg groups in patients who responded to upadacitinib 45 mg as induction treatment was 5.1 and 7.3 events per 100 patient-years, respectively. The most frequently reported serious infection in the induction and maintenance studies was gastrointestinal infections.

Malignancy

In the placebo-controlled induction studies, there were no reports of malignancy. In the placebo-controlled maintenance period, the frequency of malignancies excluding non-

melanoma skin cancer (NMSC) in the RINVOQ 15 mg and 30 mg groups was 0.5%, 1.7%, respectively, and 0.4% in the placebo group. The long-term incidence rate of malignancies excluding NMSC for RINVOQ 15 mg and 30 mg in patients who responded to upadacitinib 45 mg as induction treatment was 0.4 and 1.2 per 100 patient years, respectively.

Gastrointestinal Perforations

During the placebo-controlled period in the Phase 3 induction clinical studies, gastrointestinal perforation was reported in 1 patient (0.1%) treated with RINVOQ 45 mg and no patients on placebo through 12 weeks. In all patients treated with RINVOQ 45 mg (n=938) during the induction studies, gastrointestinal perforation was reported in 4 patients (0.4%).

In the long-term placebo-controlled maintenance period, gastrointestinal perforation was reported in 1 patient each treated with placebo (0.7 per 100 patient-years), RINVOQ 15 mg (0.4 per 100 patient-years), and RINVOQ 30 mg (0.4 per 100 patient-years). In all patients treated with rescue RINVOQ 30 mg (n=336), gastrointestinal perforation was reported in 3 patients (0.8 per 100 patient-years) through long-term treatment.

Thrombosis

In the induction studies, there were no reports of venous thrombosis (pulmonary embolism or deep vein thrombosis) in patients receiving placebo and RINVOQ 45 mg treatment. In the placebo-controlled maintenance period, the frequency of venous thrombosis over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 0% and 0.4%, respectively, and 0% in the placebo group. The long-term incidence rate of venous thrombosis for RINVOQ 15 mg and 30 mg in patients who responded to upadacitinib 45 mg as induction treatment was 0 and 0.6 per 100 patient-years, respectively.

Laboratory abnormalities

In the induction and maintenance clinical studies, the laboratory changes in ALT increased and/or AST increased (≥ 3 x ULN), CPK values (> 5 x ULN), neutropaenia (ANC < 1 x 10^9 cells/L), and lipid parameters associated with upadacitinib treatment were generally similar to what was observed in the rheumatologic disease, atopic dermatitis and ulcerative colitis clinical studies. Dose-dependent changes for these laboratory parameters associated with 15 mg and 30 mg upadacitinib treatment were observed.

In the placebo-controlled induction studies for up to 12 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 2.2% and 2.0% of patients in

the upadacitinib 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 4.6%, 5.2% and 1.8% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ALC < 0.5 x 10^9 cells/L (see section 4.2). No notable mean changes of lymphocyte counts were observed during upadacitinib treatment over time.

In the placebo-controlled induction studies for up to 12 weeks, decreases in haemoglobin concentration to below 8 g/dL in at least one measurement occurred in 2.7% and 1.4% of patients in the upadacitinib 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in haemoglobin concentration below 8 g/dL in at least one measurement occurred in 1.4%, 4.4% and 2.8% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to Hb < 8 g/dL (see section 4.2). No notable mean changes of haemoglobin concentration were observed during upadacitinib treatment over time.

Post Marketing Experience

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

- *Infections and infestations:* Diverticulitis
- *Immune system disorders:* Hypersensitivity
- *Ear and labyrinth disorders: Vertigo*
- *Reproductive system and breast disorders: Semen discolouration*

  Reports of semen discolouration (blue or green) have occurred in patients taking RINVOQ. Most reports occurred with RINVOQ 45 mg. Discolouration intensity decreased or resolved after dose reduction or discontinuation. There were no clinically meaningful adverse events reported with the semen discolouration.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Upadacitinib was administered in clinical trials up to doses equivalent in daily AUC to 60 mg modified 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 information on the management of overdose in Australia contact the Poisons Information Centre on 131126.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: L04AA44.

Mechanism of action

Janus Kinases (JAKs) are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function.

Upadacitinib is a selective and reversible inhibitor of JAK1. Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the in vivo pharmacodynamic responses, upadacitinib demonstrated 33-197-fold greater selectivity for JAK1-associated signalling over JAK2-JAK2 signalling. In enzyme assays, upadacitinib had >50-fold selectivity for JAK1 over JAK3. Atopic dermatitis pathogenesis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritis.

Pro-inflammatory cytokines (including IL-5, IL-7, IL-9, and IL-13 in ulcerative colitis and IL-2, IL-6, IL-7, IL-15, IL-21 and interferon gamma in Crohn's disease) transduce signals via the JAK1 pathway and are involved in pathology of inflammatory bowel disease. JAK1 inhibition with upadacitinib modulates the signalling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of inflammatory bowel diseases.

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 treated 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; however, the mean values at baseline and at all visits were within the normal reference range.

High-Sensitivity (hs) CRP 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 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.

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.

Clinical trials

Rheumatoid Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in five, Phase 3 randomised, double-blind, multicentre studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria (see Table 11). Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. Four studies included long-term extensions for up to 5 years and one study (SELECT-COMPARE) included a long-term extension for us to 10 years.

Table 11. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT EARLY 24-week monotherapy trial	MTX-naïve[a] (947)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	Primary Endpoint: • ACR 50 at Week 12
			Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 12 • Clinical Remission (DAS28-CRP <2.6) at Week 24 • Δ Physical Function (HAQ-DI) at Week 12 • Radiographic progression (ΔmTSS) at Week 24 Δ SF-36 PCS at Week 12
SELECT MONOTHERAPY 14-week monotherapy trial	MTX-IR[b] (648)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	Primary Endpoint: • ACR20 at Week 14
			Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 14 • Clinical Remission (DAS 28-CRP <2.6) at Week 14 • Δ Physical Function (HAQ-DI) at Week 14 • Δ SF-36 PCS at Week 14

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
			Δ Morning stiffness at Week 14
SELECT NEXT 12-week trial	csDMARD IR[c] (661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoints: • Clinical Remission (DAS28- CRP <2.6) at Week 12 • Δ Physical Function HAQ-DI at Week 12 • Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 12 • Δ SF-36 PCS at Week 12 • Δ Morning stiffness at Week 12 Δ FACIT-F at Week 12
SELECT COMPARE 48-week trial	MTX-IR[d] (1629)	• Upadacitinib 15 mg • Placebo • Adalimumab 40 mg On background MTX	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Clinical Remission (DAS28-CRP <2.6) at Week 12; • ACR50 vs adalimumab at Week 12; • Δ Physical Function (HAQ-DI) vs adalimumab at Week 12; • Δ Patient's Assessment of Pain vs adalimumab at Week 12 • Radiographic progression (ΔmTSS) at Week 26 • Δ SF-36 PCS at Week 12 • Δ Morning stiffness at Week 12 Δ FACIT-F at Week 12
SELECT BEYOND 12-week trial	bDMARD-IR[e] (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Primary Endpoint: • ACR20 at Week 12
		On background csDMARDs	Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 Δ SF-36 PCS at Week 12

Abbreviations:
ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement
bDMARD = biologic Disease-Modifying Anti-Rheumatic Drug
CRP = C-Reactive Protein
DAS28 = Disease Activity Score 28 joints
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue
mTSS = modified Total Sharp Score
csDMARD = conventional synthetic Disease-Modifying Anti-Rheumatic Drug

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
HAQ-DI = Health Assessment Questionnaire Disability Index IR = Inadequate Responder MTX = methotrexate SF-36 = Short Form (36) Health Survey PCS = Physical Component Summary [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			

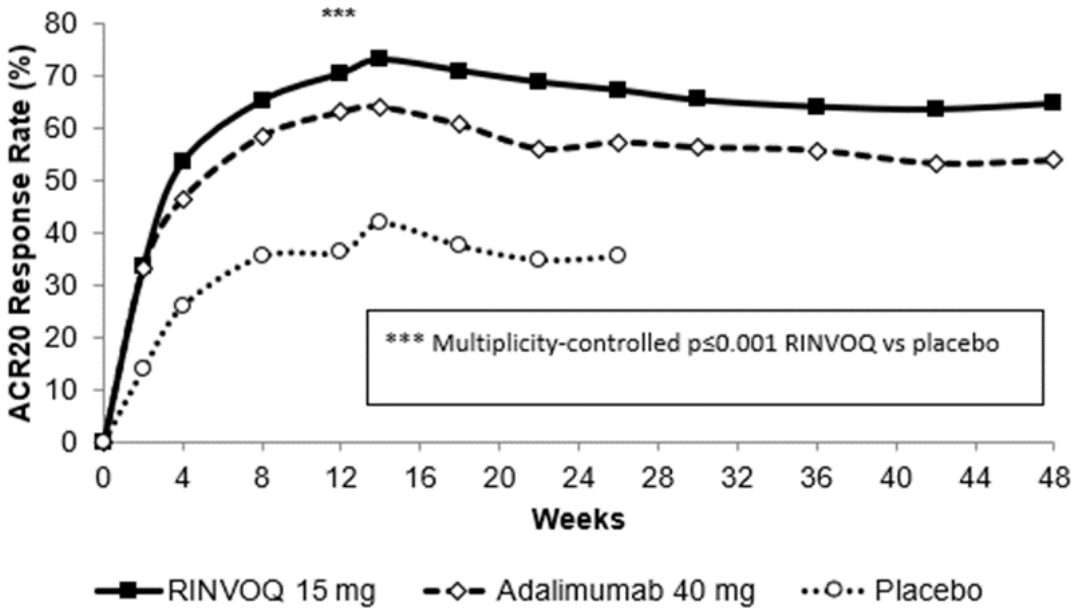
Clinical Response

ACR Response

In all studies, significantly more patients treated with RINVOQ 15 mg achieved ACR20, ACR50, and ACR70 responses at 12/14 weeks compared to placebo or MTX except for ACR70 in SELECT-BEYOND (Table 10). Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained through 3 years based on available long-term extension study results. In SELECT-COMPARE, a higher proportion of patients treated with RINVOQ 15 mg achieved ACR20 (Figure 1) and ACR70 at Weeks 12 through 48 compared to placebo or adalimumab. In a multiplicity-controlled comparison, RINVOQ was superior to adalimumab for ACR50 at Week 12.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in greater improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP, compared to placebo or MTX monotherapy. In SELECT-COMPARE, a higher proportion of patients treated with RINVOQ 15 mg achieved ACR20/50/70 at Weeks 12 through 48 compared to adalimumab. At Week 12, RINVOQ was superior to adalimumab for pain reduction in a multiplicity-controlled comparison. Greater pain reduction was seen as early as Week 1 compared to placebo and as early as Week 4 compared to adalimumab.

Figure 1. Percent of Patients Achieving ACR20 in SELECT COMPARE



Remission and low disease activity

In the studies, a significantly higher proportion of patients treated with upadacitinib 15 mg achieved low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX, or adalimumab (Table 12). Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX and were maintained through 3 years based on available long-term extension study results.

Table 12. Response and Remission

Study	SELECT EARLY MTX- Naïve		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND bDMARD-IR	
	MTX	UPA 15mg	MTX	UPA 15mg	PBO	UPA 15mg	PBO	UPA 15mg	ADA 40mg	PBO	UPA 15mg
N	314	317	216	217	221	221	651	651	327	169	164
Week											
ACR20 (% of patients)											
12[a]/14[b]	54	76[g]	41	68[e]	36	64[e]	36	71[e,i]	63	28	65[e]
24[c]/26[d]	59	79[g]					36	67[g,i]	57		
48	57	74[g]						65[i]	54		
ACR50 (% of patients)											
12[a]/14[b]	28	52[e]	15	42[g]	15	38[g]	15	45[g,h,]	29	12	34[g]
24[c]/26[d]	33	60[g]					21	54[g,i]	42		
48	43	63[g]						49[i]	40		
ACR70 (% of patients)											
12[a]/14[b]	14	32[g]	3	23[g]	6	21[g]	5	25[g,i]	13	7	12

Study	SELECT EARLY MTX- Naïve		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND bDMARD-IR	
24[c]/26[d]	18	44[g]					10	35[g,i]	23		
48	30	52[g]						36[i]	23		
LDA DAS28-CRP ≤3.2 (% of patients)											
12[a]/14[b]	28	53[f]	19	45[e]	17	48[e]	14	45[e,i]	29	14	43[e]
24[c]/26[d]	32	60[g]					18	55[e,i]	39		
48	40	62[g]						50[i]	35		
CR DAS28-CRP <2.6 (% of patients)											
12[a]/14[b]	14	36[g]	8	28[e]	10	31[e]	6	29[e,i]	18	9	29[g]
24[c]/26[d]	18	48[f]					9	41[e,i]	27		
48	30	50[g]						38[i]	28		
SDAI ≤3.3 (% of patients)											
12[a]/14[b]	6	16[g]	1	14[g]	3	10[g]	3	12[g,i]	7	5	9
24[c]/26[d]	9	28[g]					5	24[g,i]	14		
48	17	33[g]						25[i]	17		
CDAI ≤2.8 (% of patients)											
12[a]/14[b]	6	16[g]	1	13[g]	3	9[g]	3	13[g,i]	8	5	8
24[c]/26[d]	11	28[g]					6	23[g,i]	14		
48	18	33[g]						25[i]	17		

Abbreviations:
ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement;
ADA = adalimumab;
bDMARD = biologic Disease-Modifying Anti-Rheumatic Drug
CDAI = Clinical Disease Activity Index
CR = Clinical Remission
CRP = c-Reactive Protein
DAS28 = Disease Activity Score 28 joints
IR = Inadequate Responder
LDA = Low Disease Activity
MTX = methotrexate
PBO = placebo
SDAI = Simple Disease Activity Index
UPA= upadacitinib
[a] SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND
[b] SELECT-MONOTHERAPY
[c] SELECT-EARLY
[d] SELECT-COMPARE
[e] multiplicity-controlled p≤0.001upadacitinib vs placebo or MTX comparison
[f] multiplicity-controlled p≤0.01 upadacitinib vs placebo or MTX comparison
[g] nominal p≤0.05 upadacitinib vs placebo or MTX comparison
[h] multiplicity-controlled p≤0.001 upadacitinib vs adalimumab comparison
[i] nominal p≤0.05 upadacitinib vs adalimumab comparison

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 Weeks 26 and 48 (SELECT-COMPARE) and Week 24 (SELECT-EARLY).

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Weeks 26 and 48 in SELECT-COMPARE and as monotherapy compared to MTX at Week 24 in SELECT-EARLY (Table 13). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with RINVOQ 15 mg compared to placebo at Weeks 26 and 48 (SELECT-COMPARE) and compared to MTX at Week 24 (SELECT-EARLY). Inhibition of progression of structural joint damage was maintained through Week 96 in both studies for patients receiving RINVOQ 15 mg.

Table 13. Radiographic Changes

Study	**SELECT EARLY MTX-Naive**		**SELECT COMPARE MTX-IR**		
Treatment Group	MTX	UPA 15 mg	PBO[g]	UPA 15mg	ADA 40mg
Modified Total Sharps Score, mean change from baseline					
Week 24[a]/26[b]	0.7	0.1[e]	0.9	0.2[d]	0.1
Week 48			1.7	0.3[d]	0.4
Erosion Score, mean change from baseline					
Week 24[a]/26[b]	0.3	0.1[d]	0.4	0[d]	0
Week 48			0.8	0.1[d]	0.2
Joint Space Narrowing Score, mean change from baseline					
Week 24[a]/26[b]	0.3	0.1[f]	0.6	0.2[d]	0.1
Week 48			0.8	0.2[d]	0.2
Proportion of patients with no radiographic progression[c]					
Week 24[a]/26[b]	77.7	87.5[e]	76.0	83.5[e]	86.8
Week 48			74.1	86.4[d]	88.0

Abbreviations:
ADA = adalimumab
IR = Inadequate Responder
MTX = methotrexate
PBO = placebo
UPA= upadacitinib
[a] SELECT-EARLY
[b] SELECT-COMPARE
[c] No progression defined as mTSS change ≤0.
[d] p≤0.001 upadacitinib vs placebo or MTX comparison
[e] p≤0.01 upadacitinib vs placebo or MTX comparison
[f] p≤0.05 upadacitinib vs placebo or MTX comparison
[g] All placebo data at Week 48 derived using linear extrapolation

Physical Function Response and Health-Related Outcomes

Treatment with upadacitinib 15 mg, alone or in combination with csDMARDs, resulted in a significantly greater improvement in physical function compared to all comparators as measured by HAQ-DI at Week 12/14 (Table 14) with RINVOQ being superior to adalimumab in a multiplicity-controlled comparison.

Improvements in HAQ-DI and pain were maintained through 3 years for patients receiving RINVOQ 15 mg based on available results from SELECT-COMPARE and SELECT-EARLY.

Table 14. Mean change from baseline in HAQ-DI [a,b]

Study	**SELECT EARLY MTX-Naïve**		**SELECT MONO MTX-IR**		**SELECT NEXT csDMARD-IR**		**SELECT COMPARE MTX-IR**			**SELECT BEYOND BIO-IR**	
Treatment group	MTX	UPA 15mg	MTX	UPA 15mg	PBO	UPA 15mg	PBO	UPA 15mg	ADA 40mg	PBO	UPA 15mg
N	313	317	216	216	220	216	648	644	324	165	163
Baseline score, mean	1.6	1.6	1.5	1.5	1.4	1.5	1.6	1.6	1.6	1.6	1.7
Week 12[c]/14[d]	-0.5	-0.8[g]	-0.3	-0.7[g]	-0.3	-0.6[g]	-0.3	-0.6[g,i]	-0.5	-0.2	-0.4[g]
Week 24[e]/26[f]	-0.6	-0.9[h]					-0.3	-0.7[h,j]	-0.6		

Abbreviations: ADA = adalimumab; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = Inadequate Responder; MTX = methotrexate; PBO = placebo; UPA = upadacitinib

[a] Data shown are mean

[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] SELECT-EARLY, SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND

[d] SELECT-MONOTHERAPY

[e] SELECT-EARLY

[f] SELECT-COMPARE

[g] multiplicity-controlled p≤0.001 upadacitinib vs placebo or MTX comparison

[h] nominal p≤0.001 upadacitinib vs placebo or MTX comparison

[i] multiplicity-controlled p≤0.01 upadacitinib vs adalimumab comparison

[j] nominal p≤0.01 upadacitinib vs adalimumab comparison

In the studies SELECT-MONOTHERAPY, SELECT-NEXT, and SELECT-COMPARE, treatment with upadacitinib 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.

In the clinical studies, upadacitinib treated patients reported significant improvements in patient-reported quality of life, as measured by the Short Form (36) Health Survey (SF-36) Physical Component Score compared to placebo and MTX. Moreover, upadacitinib treated patients reported significant improvements in fatigue at Week 12, as measured by the

Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) compared to placebo.

Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in two Phase 3 randomised, double-blind, multicentre, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis (Table 15). 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. In SELECT-PsA 1, 81.7% of participants were taking stable doses of at least one non-biological DMARD (predominantly methotrexate) at baseline. In SELECT-PsA 2, 46.2% of participants were taking stable doses of at least one non-biological DMARD at baseline. The studies include long-term extensions for up to 5 years (SELECT-PsA 1) and 3 years (SELECT-PsA 2).

Table 15. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-PsA 1	Non-biological DMARD-IR[a] (1705)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo • Adalimumab 40 mg	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoints: • MDA at Week 24 • Resolution of enthesitis (LEI=0) and dactylitis (LDI=0) at Week 24 • PASI75 at Week 16 • sIGA at Week 16 • SAPS at Week 16 • Radiographic progression (ΔmTSS) at Week 24 • Δ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS at Week 12 • FACIT-F at Week 12 • ACR20, pain, and Δ Physical Function (HAQ-DI) vs adalimumab at Week 12
SELECT-PsA 2	bDMARD-IR[b] (642)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoints: •MDA at Week 24 •PASI75 at Week 16 •sIGA at Week 16 •SAPS at Week 16 •Δ Physical Function (HAQ-DI) at Week 12 •SF-36 PCS at Week 12 •FACIT-F at Week 12

Abbreviations:
ACR20 = American College of Rheumatology ≥20% improvement
bDMARD = biological Disease-Modifying Anti-Rheumatic Drug
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue score
HAQ-DI = Health Assessment Questionnaire-Disability Index
IR = Inadequate Responder
MDA = Minimal Disease Activity
mTSS = modified Total Sharp Score

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
PASI = Psoriasis Area and Severity Index SAPS = Self-Assessment of Psoriasis Symptoms SF-36 PCS = Short Form (36) Health Survey (SF-36) Physical Component Summary sIGA = static Investigator Global Assessment of psoriasis [a] Patients who had an inadequate response or intolerance to at least one non-biological DMARD [b] Patients who had an inadequate response or intolerance to at least one bDMARD			

Clinical Response

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved ACR20 response compared to placebo at Week 12 (Table 16, Figure 2). In SELECT PsA 1, RINVOQ 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at Week 12. A higher proportion of patients treated with RINVOQ 15 mg achieved ACR50 and ACR70 responses at Week 12 compared to placebo. Time to onset of efficacy was rapid across measures with greater responses 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 (Table 17). Treatment with RINVOQ 15 mg resulted in greater improvement in pain compared to adalimumab at Week 24.

In both studies, consistent responses were observed alone or in combination with non-biological DMARDs for primary and key secondary endpoints.

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

Figure 2. Percent of Patients Achieving ACR 20 in SELECT- PsA 1

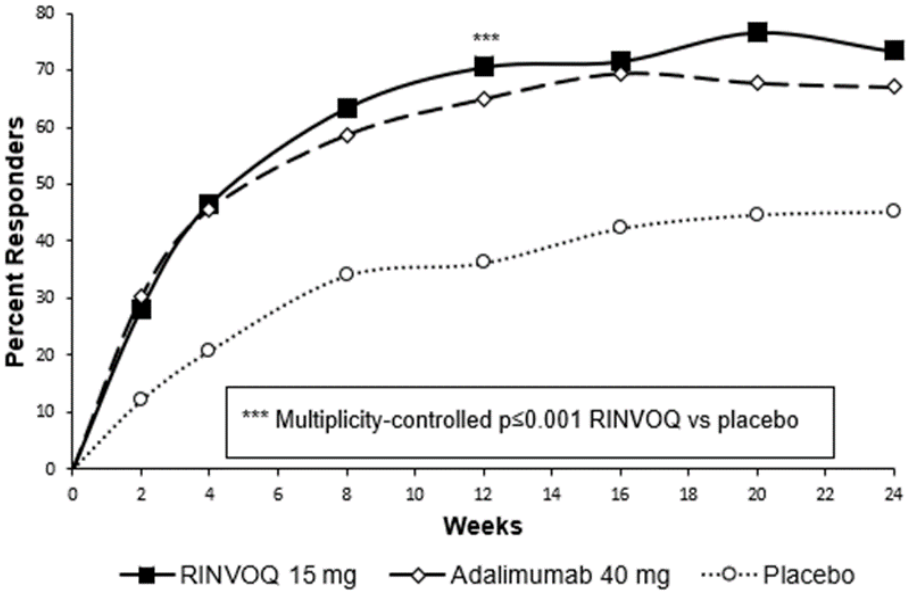


Table 16. Clinical Response

Study	**SELECT-PsA 1 non-biological DMARD-IR**			**SELECT-PsA 2 bDMARD-IR**	
Treatment Group	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 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,h]	67	20	59[f]
ACR50 (% of patients)					
Week 12	13	38[f]	38	5	32[f]
Week 24	19	52[f,h]	44	9	38[f]
ACR70 (% of patients)					
Week 12	2	16[f]	14	1	9[f]
Week 24	5	29[f,h]	23	1	19[f]
MDA (% of patients)					
Week 12	6	25[f]	25	4	17[f]
Week 24	12	37[e]	33	3	25[e]
Resolution of enthesitis (LEI=0; % of patients)[a]					
Week 12	33	47[f]	47	20	39[f]
Week 24	32	54[e]	47	15	43[f]
Resolution of dactylitis (LDI=0; % of patients)[b]					
Week 12	42	74[f]	72	36	64[g]
Week 24	40	77[f]	74	28	58[g]
PASI75 (% of patients)[c]					
Week 16	21	63[e]	53	16	52[e]
Week 24	27	64[f]	59	19	54[f]

Study	SELECT-PsA 1 non-biological DMARD-IR			SELECT-PsA 2 bDMARD-IR	
Treatment Group	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
PASI90 (% of patients)[c]					
Week 16	12	38[f]	39	8	35[f]
Week 24	17	42[f]	45	7	36[f]
PASI100 (% of patients)[c]					
Week 16	7	24[f]	20	6	25[f]
Week 24	10	27[f]	28	5	22[f]
sIGA 0/1 (% of patients)[d]					
Week 16	11	42[e]	39	9	37[e]
Week 24	12	45[f]	41	10	33[f]

Abbreviations:
ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement
ADA = adalimumab
bDMARD = biological Disease-Modifying Anti-Rheumatic Drug
IR = Inadequate Responder
MDA = Minimal Disease Activity
PASI75 (or 90 or 100) = ≥75% (or ≥90% or 100%) improvement in Psoriasis Area and Severity Index
PBO = placebo
sIGA = static Physician Global Assessment
UPA= upadacitinib
Patients who discontinued randomised 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, for SELECT-PsA 1 and n=144 and 133, respectively, for SELECT-PsA 2)
[b] In patients with dactylitis at baseline (n=126, 136, and 127, respectively, for SELECT-PsA 1 and n=64 and 55, respectively, for SELECT-PsA 2)
[c] In patients with ≥ 3% BSA psoriasis at baseline (n=211, 214, and 211, respectively, for SELECT-PsA 1 and n=131 and 130, respectively, for SELECT-PsA 2)
[d] In patients with sIGA ≥ 2 at baseline (n=313, 322, and 330, respectively, for SELECT-PsA 1 and n=163 and 171, respectively, for SELECT-PsA 2)
[e] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[f] nominal p≤0.001 upadacitinib vs placebo comparison
[g] nominal p≤0.01 upadacitinib vs placebo comparison
[h] nominal p<0.05 upadacitinib vs adalimumab comparison

Table 17. Components of ACR Response (mean change from baseline)

Study	SELECT-PsA 1 non-biological DMARD-IR			SELECT-PsA 2 bDMARD-IR	
Treatment Group	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
Number of tender/painful joints (0-68)					
Week 12	-7.1	-11.3	-10.3	-6.2	-12.4
Week 24	-9.2	-13.7	-12.5	-6.6	-14.0
Number of swollen joints (0-66)					
Week 12	-5.3	-7.9	-7.6	-4.8	-7.1
Week 24	-6.3	-9.0	-8.6	-5.6	-8.3
Patient assessment of pain[a]					
Week 12	-0.9	-2.3	-2.3	-0.5	-1.9
Week 24	-1.4	-3.0	-2.6	-0.7	-2.2
Patient global assessment[a]					
Week 12	-1.2	-2.7	-2.6	-0.6	-2.3
Week 24	-1.6	-3.4	-2.9	-0.8	-2.6
Disability index (HAQ-DI)[b]					
Week 12	-0.14	-0.42	-0.34	-0.10	-0.30
Week 24	-0.19	-0.51	-0.39	-0.08	-0.33
Physician global assessment[a]					
Week 12	-2.1	-3.6	-3.4	-1.4	-3.1
Week 24	-2.8	-4.3	-4.1	-1.8	-3.8
hsCRP (mg/L)					
Week 12	-1.3	-7.1	-7.6	0.3	-6.6
Week 24	-2.1	-7.6	-7.3	-0.9	-6.3

Abbreviations:
ACR = American College of Rheumatology
ADA = adalimumab
hsCRP = high sensitivity C-Reactive Protein
HAQ-DI = Health Assessment Questionnaire-Disability Index
IR = Inadequate Responder
PBO = placebo
UPA = upadacitinib
[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.

In both studies, response rates for ACR20/50/70, MDA, PASI75/90/100, sIGA, enthesitis resolution, and dactylitis resolution in patients treated with RINVOQ 15 mg were maintained through Week 56.

Radiographic Response

In SELECT-PsA 1, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Total Sharp Score

(mTSS) and its components, the erosion score and the joint space narrowing score, at Week 24.

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Week 24 (Table 18). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0.5) was higher with RINVOQ 15 mg compared to placebo at Week 24.

Table 18. Radiographic Changes in SELECT-PsA 1

Treatment Group	PBO	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline			
Week 24	0.25	-0.04[b]	0.01
Erosion Score, mean change from baseline			
Week 24	0.12	-0.03[c]	0.01
Joint Space Narrowing Score, mean change from baseline			
Week 24	0.10	-0.00[d]	-0.02
Proportion of patients with no radiographic progression[a]			
Week 24	92	96[d]	95

Abbreviations:
ADA = adalimumab; PBO = placebo; UPA= upadacitinib
[a] No progression defined as mTSS change ≤0.5
[b] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[c] nominal p≤0.001 upadacitinib vs placebo comparison
[d] nominal p<0.05 upadacitinib vs placebo comparison

Physical Function Response and Health-Related Outcomes

In both studies, patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by HAQ-DI at Week 12 (Table 17), which was maintained through Week 56.

The proportion of HAQ-DI responders (≥ 0.35 improvement from baseline in HAQ-DI score) at Week 12 in SELECT-PsA 1 and SELECT-PsA 2 was 58% and 45%, respectively, in patients receiving RINVOQ 15 mg, 33% and 27%, respectively, in patients receiving placebo, and 47% in patients receiving adalimumab (SELECT-PsA 1).

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. Greater improvement was also observed compared to adalimumab. Greater improvement was observed in the Mental

Component Summary score and all 8 domains of SF-36 (Physical Functioning, Bodily Pain, Vitality, Social Functioning, Role Physical, General Health, Role Emotional, and Mental Health) compared to placebo. 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.

Greater improvement in patient-reported psoriasis symptoms, as measured by the Self-Assessment of Psoriasis Symptoms (SAPS), was observed in both studies at Week 16 in patients treated with RINVOQ 15 mg compared to placebo and adalimumab. Improvements from baseline were maintained through Week 56 in both studies.

Among patients with psoriatic spondylitis, in both studies patients treated with RINVOQ 15 mg showed improvements from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) compared to placebo at Week 24. Greater improvements were also observed compared to adalimumab. Improvements from baseline were maintained through Week 56 in both studies.

Non-radiographic Axial Spondyloarthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in a randomised, double-blind, multicenter, placebo-controlled study in patients 18 years of age or older with active non-radiographic axial spondyloarthritis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, Patient's Assessment of Total Back Pain score ≥ 4, and objective signs of inflammation (Table 17). The study included a long-term extension for up to 2 years.

Table 19. Clinical Trial Summary

Study Name	Population (n)[a]	Treatment Arms	Key Outcome Measures
SELECT-AXIS 2 (STUDY 2)	NSAID-IR[b,c] (314)	• Upadacitinib 15 mg • Placebo	Primary Endpoint: • ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASDAS-CRP • SPARCC MRI score (SI joints) • BASDAI 50 • ASDAS Inactive Disease • Total Back Pain • Nocturnal Back Pain • ASDAS Low Disease Activity • ASAS Partial Remission • BASFI (function) • AS Quality of Life • ASAS Health Index • ASAS20 • BASMI (spinal mobility) • MASES (enthesitis)

Abbreviations: ASAS40 = Assessment of SpondyloArthritis international Society ≥40% improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; NSAID = Nonsteroidal Anti-inflammatory Drug; SPARCC MRI = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging

[a] 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.

[b] Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindication for NSAIDs

[c] At baseline, 29.1% of the patients were on a concomitant csDMARD and 32.9% of the patients had an inadequate response or intolerance to bDMARD therapy.

Clinical Response

In SELECT-AXIS 2 (STUDY 2), a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 20, Figure 3). Time to onset of efficacy was rapid with responses seen as early as Week 2 for ASAS40.

Treatment with RINVOQ 15 mg resulted in greater improvement in individual ASAS components (patient global assessment of disease activity, total back pain assessment, inflammation, and function) and other measures of disease activity, including BASDAI compared to placebo at Week 14.

The efficacy of RINVOQ 15 mg was demonstrated across subgroups including gender, baseline BMI, symptom duration of non-radiographic axial spondyloarthritis, baseline hsCRP, MRI sacroiliitis, and prior use of bDMARDs.

Figure 3. Percent of Patients Achieving ASAS40

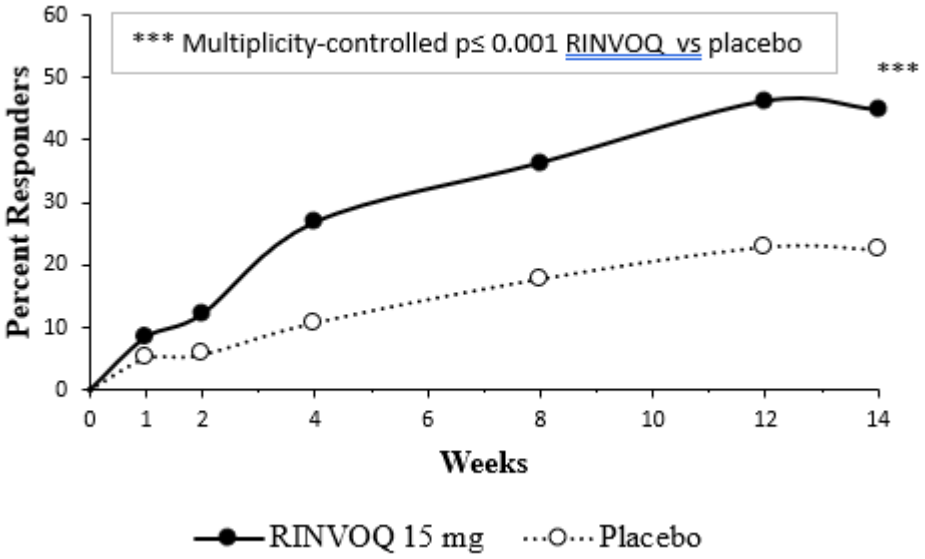


Table 20. Clinical Response at Week 14

	PBO (N=157)	UPA 15 mg (N=156)
ASAS40 (%)		
Week 14	22.5	44.9[a]
Week 52	42.7	62.8[c]
ASAS20 (%)		
Week 14	43.8	66.7[a]
Week 52	52.2	68.6[d]
ASAS Partial Remission (%)		
Week 14	7.6	18.6[b]
Week 52	17.8	35.3[c]
BASDAI 50 (%)		
Week 14	22.1	42.3[a]
Week 52	40.1	55.8[d]
ASDAS-CRP (Change from baseline)		
Week 14	-0.71	-1.36[a]
Week 52	-1.23	-1.8[c]
ASDAS Inactive Disease (%)		
Week 14	5.2	14.1[b]
Week 52	10.8	32.7[c]
ASDAS Low Disease Activity (%)		
Week 14	18.3	42.3[a]
Week 52	32.5	55.8[c]

[a] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[b] multiplicity-controlled p≤0.01 upadacitinib vs placebo comparison
[c] nominal p≤0.001 upadacitinib vs placebo comparison
[d] nominal p≤0.01 upadacitinib vs placebo comparison
For binary endpoints, results are based on non-responder imputation in conjunction with multiple imputation. For continuous endpoints, results are based on the least squares mean change from baseline using mixed models for repeated measures analysis.

Efficacy was maintained through 2 years as assessed by the endpoints presented in Table 20.

In SELECT-AXIS 2 (STUDY 2), efficacy was maintained through Week 52 as assessed by the endpoints presented in Table 18.

Table 21. Components of ASAS Response (mean change from baseline)

Treatment Group	PBO (N=157)	UPA 15 mg (N=156)
Patient Global Assessment of Disease Activity[a]		
Week 14	-1.87	-2.89[d]
Week 52	-3.30	-4.27[d]
Total Back Pain[a]		
Week 14	-2.00	-2.91[c]
Week 52	-3.46	-4.22[e]
BASFI[a]		
Week 14	-1.47	-2.61[c]
Week 52	-2.74	-3.71[d]
Inflammation[b]		
Week 14	-1.93	-3.05[d]
Week 52	-3.38	-4.03[e]

Results are based on the least squares mean change from baseline using mixed models for repeated measures analysis
[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 upadacitinib vs placebo comparison
[d] nominal p≤0.001 upadacitinib vs placebo comparison
[e] nominal p≤0.05 upadacitinib vs placebo comparison

Physical Function Response and Health-Related Outcomes

Patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by the BASFI at Week 14 (Table 21).

Patients treated with RINVOQ 15 mg showed significant improvements in total back pain and nocturnal back pain compared to placebo at Week 14.

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.

Improvements in BASFI, total and nocturnal back pain, and ASQoL, ASAS Health Index and FACIT-F were maintained through 2 years.

Enthesitis

Patients with pre-existing enthesitis treated with RINVOQ 15 mg showed greater improvement in enthesitis compared to placebo as measured by change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Week 14. Improvement in enthesitis was maintained through 2 years.

Objective Measures of Inflammation

Signs of inflammation were assessed by MRI and expressed as change from baseline in the SPARCC score. Improvement of inflammatory signs in both sacroiliac joints and the spine was observed in patients treated with upadacitinib 15 mg. At Week 14, significant improvement of inflammatory signs in the sacroiliac joints was observed in patients treated with upadacitinib 15 mg compared to placebo.

Improvement in inflammation as assessed by MRI was maintained through 2 years.

Ankylosing Spondylitis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in two randomised, double-blind, multicentre, 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 (Table 22). Both studies included a long-term extension for up to 2 years.

Table 22. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-AXIS 1	NSAID-IR[a,b] bDMARD-naïve (187)	• Upadacitinib 15 mg • Placebo	Primary Endpoint: • ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASAS Partial Remission • BASDAI 50 • ASDAS-CRP • BASFI • SPARCC MRI score (spine)
SELECT-AXIS 2 (STUDY 1)	bDMARD-IR[a,c,d] (420)	• Upadacitinib 15 mg • Placebo	Primary Endpoint: • ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASDAS-CRP • SPARCC MRI score (spine) • BASDAI 50 • ASAS20 • ASDAS Inactive Disease • Total Back Pain • Nocturnal Back Pain • ASDAS Low Disease Activity • BASFI (function) • ASAS Partial Remission • AS Quality of Life • ASAS Health Index • BASMI (spinal mobility) • MASES (enthesitis)

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
Abbreviations: ASAS40 = Assessment of SpondyloArthritis international Society ≥40% improvement ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein BASDAI = Bath Ankylosing Spondylitis Disease Activity Index BASFI = Bath Ankylosing Spondylitis Functional Index bDMARD = biological Disease-Modifying Anti-Rheumatic Drug IR = Inadequate Responder NSAID = Nonsteroidal Anti-inflammatory Drug SPARCC MRI = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging [a]Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindication for NSAIDs [b]At baseline, approximately 16% of the patients were on a concomitant csDMARD. [c] Patients who had an inadequate response or intolerance to one or two bDMARDs [d.]At baseline, approximately 31% of the patients were on a concomitant csDMARD			

Clinical Response

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 23, Figures 4 and 5). Time to onset of efficacy was rapid across measures, with greater responses seen as early as Week 2 in SELECT-AXIS 1 and Week 4 in SELECT-AXIS 2 (STUDY 1) for ASAS40.

Treatment with RINVOQ 15 mg resulted in improvements in individual ASAS components (patient global assessment of disease activity, total back pain assessment, inflammation, and function) and other measures of disease activity, including BASDAI at Week 14 compared to placebo (Table 24).

The efficacy of RINVOQ 15 mg was demonstrated regardless of subgroups evaluated including gender, baseline BMI, symptom duration of ankylosing spondylitis, baseline hsCRP, and prior use of bDMARDs (N.B., subjects who had lack of efficacy to both TNFi and IL-17i therapy were not included in the study).

Figure 4. Percent of Patients Achieving ASAS 40 in SELECT-AXIS 1

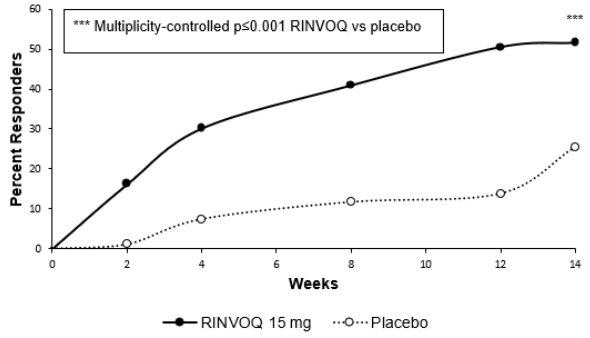


Figure 5. Percent of Patients Achieving ASAS40 in SELECT-AXIS 2 (STUDY 1)

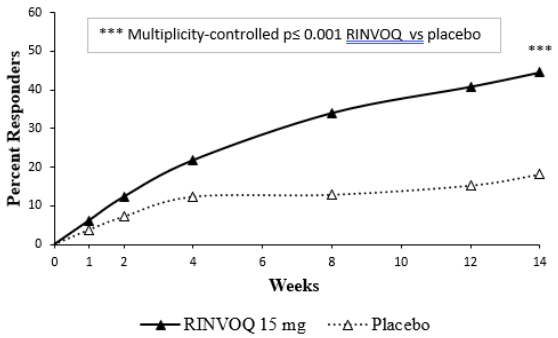


Table 23. Clinical Response

Study	SELECT-AXIS 1 bDMARD-naïve		SELECT-AXIS 2 (STUDY 1) bDMARD-IR	
Treatment Group	**PBO**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
N	94	93	209	211
ASAS40 (% of patients)				
Week 14	25.5	51.6[a]	18.2	44.5[a]
Week 52		80.2		73.7
Week 104		85.9		81.5
ASAS20 (% of patients)				
Week 14	40.4	64.5[c]	38.3	65.4 [a]
Week 52		87.7		88.7
Week 104		90.1		91.1
ASAS Partial Remission (% of patients)				
Week 14	1.1	19.4[a]	4.3	17.5 [a]
Week 52		50.0		33.5
Week 104		51.4		42.9
BASDAI 50 (% of patients)				
Week 14	23.4	45.2[b]	16.7	43.1 [a]
Week 52		77.8		64.9
Week 104		88.7		78.6
ASDAS-CRP (Change from baseline)				
Week 14	-0.54	-1.45[a]	-0.49	-1.52 [a]
Week 52		-2.05		-2.01
Week 104		-2.10		-2.23
ASDAS Inactive Disease (% of patients)				
Week 14	0	16.1[c]	1.9	12.8 [a]
Week 52		46.2		30.4
Week 104		45.6		38.0
ASDAS Low Disease Activity (% of patients)[d]				
Week 14	10.6	49.5[c, d]	10.1	44.1 [a]
Week 52		85.9		65.8
Week 104		86.8		71.1

Study	SELECT-AXIS 1 bDMARD-naïve	SELECT-AXIS 2 (STUDY 1) bDMARD-IR

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
UPA= upadacitinib
[a] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[b] multiplicity-controlled p≤0.01 upadacitinib vs placebo comparison
[c] nominal p≤0.001 upadacitinib vs placebo comparison
[d] post-hoc analysis for SELECT-AXIS 1
For binary endpoints, Week 14 results are based on non-responder imputation (SELECT-AXIS 1) and on non-responder imputation in conjunction with multiple imputation (SELECT-AXIS 2 [STUDY 1]). For continuous endpoints, Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measure analysis. For binary and continuous endpoints, Week 52 and Week 104 results are based on as-observed data.

In both studies (SELET-AXIS 1 and SELECT-AXIS 2 (Study 1)), efficacy was maintained: through 2 years as assessed by the endpoints presented in Table 23.

Table 24. Components of ASAS Response (mean change from baseline)

Study	SELECT-AXIS 1 bDMARD-naive		SELECT-AXIS 2 (STUDY 1) bDMARD-IR	
Treatment Group	**PBO**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
N	94	93	209	211
Patient Global Assessment of Disease Activity[a]				
Week 14	-1.31	-2.96[d]	-1.38	-2.97[d]
Week 52		-4.54		-4.62
Week 104		-4.68		-5.14
Total Back Pain[a]				
Week 14	-1.68	-3.21[d]	-1.47	-3.00[c]
Week 52		-4.75		-4.60
Week 104		-4.79		-5.08
BASFI[a]				
Week 14	-1.30	-2.29[c]	-1.09	-2.26[c]
Week 52		-3.71		-3.68
Week 104		-3.76		-4.02
Inflammation[b] (0-10)				
Week 14	-1.90	-3.15[d]	-1.59	-2.94[d]
Week 52		-4.80		-4.30
Week 104		-4.89		-4.72

Abbreviations:
ASAS = Assessment of SpondyloArthritis international Society
BASFI = Bath Ankylosing Spondylitis Functional Index
PBO = placebo
UPA= upadacitinib
Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis; Week 52 and Week 104 results are based on as-observed data.
[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 upadacitinib vs placebo comparison
[d] nominal p≤0.001 upadacitinib vs placebo comparison

Physical Function and Health-Related Outcomes

In both studies, patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by the BASFI at Week 14 (Table 24).

In SELECT-AXIS 1, patients treated with RINVOQ 15 mg showed greater improvement in back pain as assessed by the Total Back Pain component of ASAS response and nocturnal back pain compared to placebo at Week 14.

In SELECT-AXIS 2 (STUDY 1), patients treated with RINVOQ 15 mg showed significant improvements in total back pain and nocturnal back pain compared to placebo at Week 14.

In both studies, improvement in the overall level of neck, back, or hip pain was demonstrated using BASDAI Question 2. Improvements were also demonstrated for peripheral pain and swelling (assessed by BASDAI question 3 on overall pain in joints other than in the neck, back, or hips).

In both studies (SELECT-AXIS 1 and SELECT-AXIS 2 (Study 1), improvements in BASFI and pain were maintained through 2 years, for patients receiving RINVOQ 15 mg.

In both studies (SELECT-AXIS 1 and SELECT-AXIS 2 (Study 1), patients treated with RINVOQ 15 mg showed 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 maintained through 2 years.

In SELECT-AXIS 2 (STUDY 1), patients treated with RINVOQ 15 mg experienced greater improvement from baseline in fatigue as measured by FACIT-F score compared to placebo at Week 14. Improvement in FACIT-F was maintained through 2 years.

Enthesitis

In SELECT-AXIS 2 (STUDY 1), 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 MASES at week 14, which was maintained through week 52. Improvements in MASES were also observed in SELECT-AXIS 1 compared to placebo at Week 14. Improvement in enthesitis was maintained through 2 years.

Spinal mobility

In SELECT-AXIS 2 (STUDY 1), 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 which was maintained through week 52. Improvements in BASMI were also observed in SELECT-AXIS 1 compared to placebo at Week 14. Improvement in BASMI was maintained through 2 years.

Objective Measures of Inflammation

Signs of inflammation were assessed by MRI and expressed as change from baseline in the SPARCC score for spine and sacroiliac joints. In both studies (SELECT-AXIS 1 and SELECT-AXIS 2 (Study 1)), at Week 14, significant improvement of inflammatory signs in the spine was observed in patients treated with RINVOQ 15 mg compared to placebo. Additionally, patients treated with RINVOQ 15 mg demonstrated greater improvement of inflammatory signs in sacroiliac joints compared to placebo. improvement in inflammation as assessed by MRI was maintained through 2 years.

Atopic Dermatitis

The efficacy and safety of RINVOQ 15 mg and 30 mg once daily was assessed in three Phase 3 randomised, double-blind, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 2584 patients (12 years of age and older) (Table 25). RINVOQ was evaluated in 344 adolescent and 2240 adult patients with moderate to severe atopic dermatitis, not adequately controlled by topical medication(s). At baseline, patients had to have all the following: an Investigator's Global Assessment (vIGA-AD) score ≥3 in the overall assessment of atopic dermatitis (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 doses of 15 mg, 30 mg or matching placebo for 16 weeks. In the AD UP study, patients also received concomitant topical corticosteroids (TCS).

Following completion of the double-blinded period, patients originally randomised to RINVOQ were to continue receiving the same dose until week 136. Patients in the placebo group were re-randomised in a 1:1 ratio to receive RINVOQ 15 mg or 30 mg until Week 136.

Table 25. Clinical Trial Summary

Study Name	Treatment Arms	Key Outcome Measures
MEASURE UP 1 and MEASURE UP 2	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Co-Primary Endpoints at Week 16: • EASI 75 • vIGA-AD 0/1
		Key Secondary Endpoints (at Week 16 except where noted) • EASI 90/100 • EASI 75 at Week 2 • % change in EASI • % change in SCORAD • Worst Pruritus NRS improvement ≥ 4 at Week 1 and 16 • Worst Pruritus NRS improvement ≥ 4 at Day 2 (30mg), Day 3 (15mg) • % change in Worst Pruritus NRS • EASI increase ≥ 6.6 points (flare) during double-blind period • ADerm-SS TSS-7 improvement ≥ 28 • ADerm-SS Skin Pain improvement ≥ 4 • ADerm-IS Sleep improvement ≥ 12 • ADerm-IS Emotional State improvement ≥ 11 • ADerm-IS Daily Activities improvement ≥ 14 • POEM improvement ≥ 4 • HADS-A < 8 and HADS-D < 8 • DLQI 0/1 • DLQI improvement ≥ 4
AD UP	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Co-Primary Endpoints at Week 16: • EASI 75 • vIGA-AD 0/1
		Key Secondary Endpoints (at Week 16 except where noted) • EASI 75 at Week 2 and 4 • EASI 90 at Week 4 and 16 • EASI 100 (30mg) • % change in EASI • Worst Pruritus NRS improvement ≥ 4 at Week 1, 4 and 16 • % change in Worst Pruritus NRS
Abbreviations: SCORAD = SCORing Atopic Dermatitis POEM = Patient Oriented Eczema Measure DLQI = Dermatology Life Quality Index HADS = Hospital Anxiety and Depression Scale ADerm-SS = Atopic Dermatitis Symptom Scale ADerm-IS = Atopic Dermatitis Impact Scale		

Clinical Response

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 achieved vIGA-AD 0 or 1 response and achieved EASI 75 compared to placebo at Week 16 (Table 26). A rapid improvement in skin clearance (defined as EASI 75 by Week 2) was achieved for both doses compared to placebo ($p < 0.001$).

A significantly greater proportion of patients treated with RINVOQ 15 mg or 30 mg achieved clinically meaningful improvement in itch (defined as a ≥ 4-point reduction in the Worst Pruritus NRS) compared to placebo at Week 16. Rapid improvement in itch (defined as a ≥ 4-point reduction in Worst Pruritus NRS by Week 1) was achieved for both doses compared to placebo ($p < 0.001$), with differences observed as early as 1 day after initiating RINVOQ 30 mg (Day 2, $p < 0.001$) and 2 days after initiating RINVOQ 15 mg (Day 3, $p < 0.001$).

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 (increase in EASI by ≥ 6.6), during the initial 16 weeks of treatment compared to placebo ($p < 0.001$).

Figure 6 and Figure 7 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.

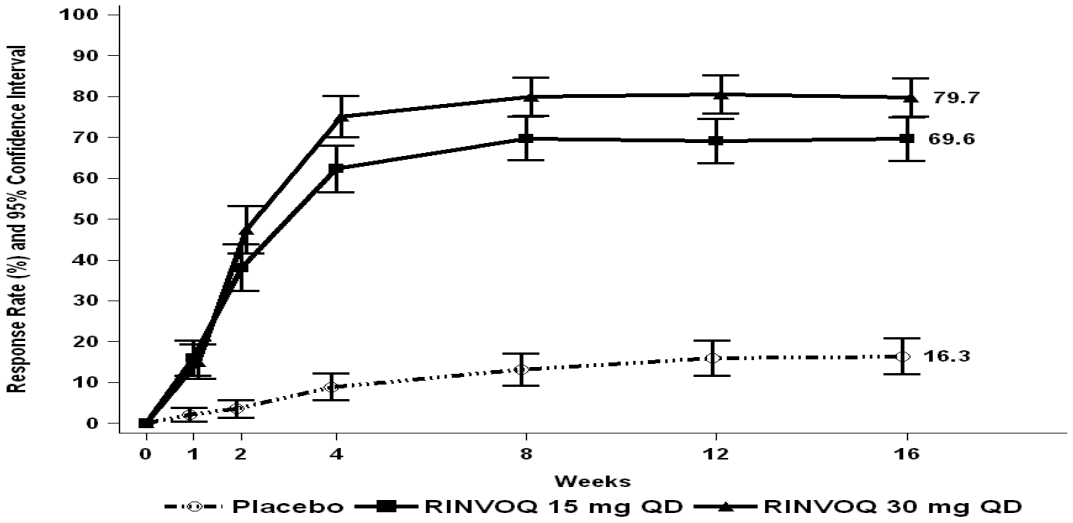
Table 26. Efficacy results of RINVOQ monotherapy studies at Week 16

Study	**MEASURE UP 1**			**MEASURE UP 2**		
Treatment Group	PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg
Number of subjects randomised	281	281	285	278	276	282
% responders						
vIGA-AD 0/1[a,b]	8.4	48.1[f]	62.0[f]	4.7	38.8[f]	52.0[f]
EASI 75[a]	16.3	69.6[f]	79.7[f]	13.3	60.1[f]	72.9[f]
EASI 90[a]	8.1	53.1[f]	65.8[f]	5.4	42.4[f]	58.5[f]
EASI 100[a]	1.8	16.7[f]	27.0[f]	0.7	14.1[f]	18.8[f]
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	11.8 N=272	52.2[f] N=274	60.0[f] N=280	9.1 N=274	41.9[f] N=270	59.6[f] N=280
Worst Pruritus NRS 0 or 1[d]	5.5 N=275	36.6[g] N=279	47.5[g] N=282	4.3 N=277	26.9[g] N=275	44.1[g] N=281
Mean percent change (SE)[e]						
EASI	-40.7 (2.28)	-80.2[f] (1.91)	-87.7[f] (1.87)	-34.5 (2.59)	-74.1[f] (2.20)	-84.7[f] (2.18)
SCORAD	-32.7 (2.33)	-65.7[f] (1.78)	-73.1[f] (1.73)	-28.4 (2.50)	-57.9[f] (2.01)	-68.4[f] (2.04)
Worst Pruritus NRS	-26.1 (5.41)	-62.8[f] (4.49)	-72.0[f] (4.41)	-17.0 (2.73)	-51.2[f] (2.34)	-66.5[f] (2.31)

Abbreviations:
UPA= upadacitinib (RINVOQ); PBO = placebo
[a] Based on number of subjects randomised
[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] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4
[d] N = number of patients whose baseline Worst Pruritus NRS is > 1
[e] % change = least squares mean percent change relative to baseline
[f] multiplicity-controlled $p < 0.001$ upadacitinib vs placebo comparison
[g] nominal $p<0.001$ upadacitinib vs placebo comparison

Figure 6. Proportion of patients achieving an EASI 75 response in monotherapy studies

MEASURE UP 1



MEASURE UP 2

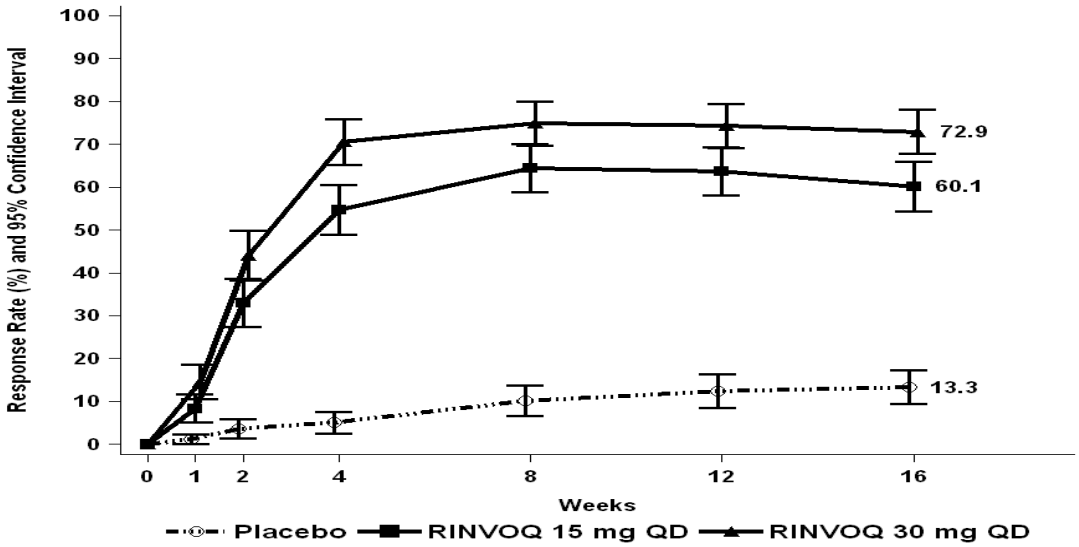
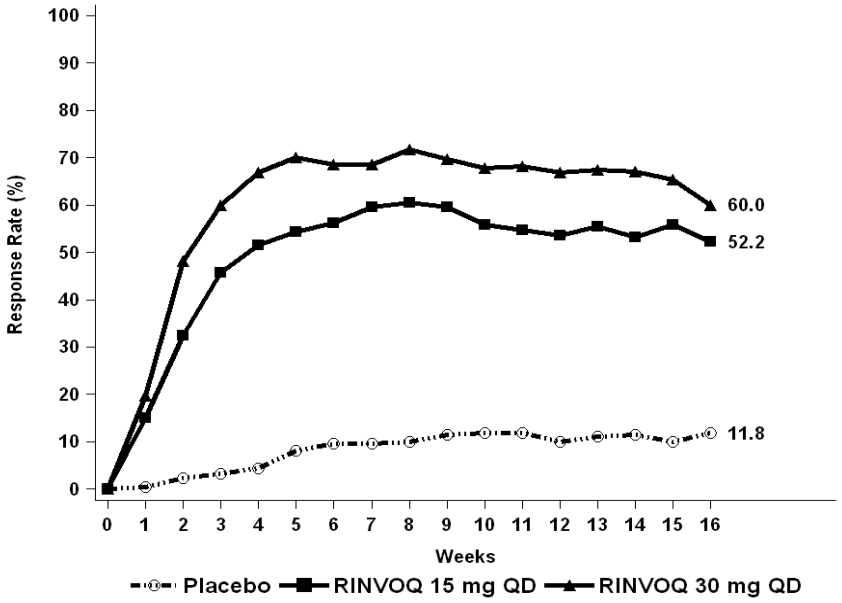
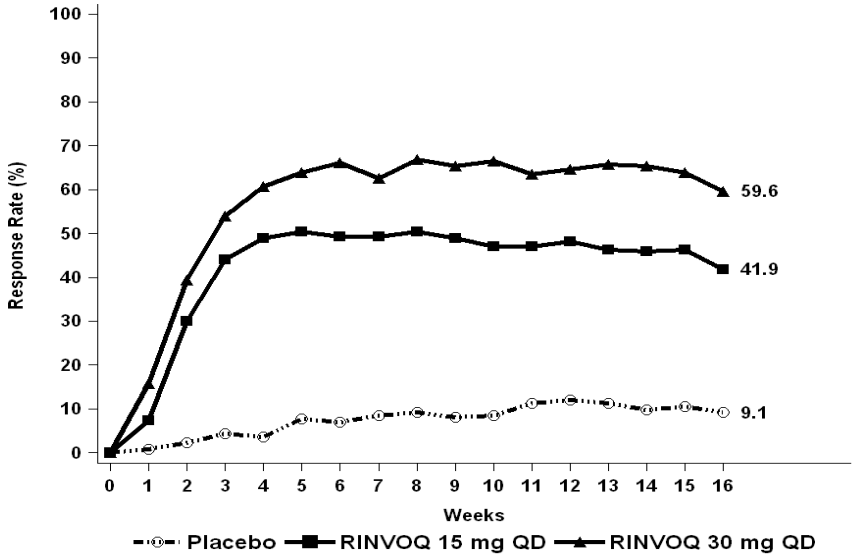


Figure 7. Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in monotherapy studies

MEASURE UP 1



MEASURE UP 2]



In both studies, results at Week 16 continued to be observed through Week 52 in patients treated with RINVOQ 15 mg or 30 mg.

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 achieved EASI 75 compared to placebo + TCS at Week 16 (Table 27). A rapid improvement in skin clearance (defined as EASI 75 by Week 2) was achieved for both doses compared to placebo + TCS ($p < 0.001$). In addition, a higher EASI 90 response rate was achieved at Week 4 for both doses compared to placebo + TCS ($p < 0.001$).

A significantly greater proportion of patients treated with RINVOQ 15 mg + TCS or 30 mg + TCS achieved a clinically meaningful improvement in itch (defined as a ≥ 4-point reduction in the Worst Pruritus NRS) compared to placebo + TCS at Week 16. A rapid improvement in itch (defined as a ≥ 4-point reduction in Worst Pruritus NRS by Week 1) was achieved for both doses compared to placebo + TCS ($p < 0.001$).

Figure 8 and Figure 9 show the proportion of patients achieving an EASI 75 response and the proportion of patients with ≥4-point improvement in Worst Pruritus NRS, respectively up to Week 16.

Table 27. Efficacy results of RINVOQ + concomitant TCS at Week 16

Treatment Group	Placebo + TCS	UPA 15 mg + TCS	UPA 30 mg + TCS
Number of subjects randomised	304	300	297
% responders			
vIGA-AD 0/1[a,b]	10.9	39.6[f]	58.6[f]
EASI 75[a]	26.4	64.6[f]	77.1[f]
EASI 90[a]	13.2	42.8[f]	63.1[f]
EASI 100[a]	1.3	12.0[g]	22.6[f]
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	15.0 N=294	51.7[f] N=288	63.9[f] N=291
Worst Pruritus NRS 0 or 1[d]	7.3 N=300	33.1[g] N=296	43.0[g] N=293
Mean percent change (SE)[e]			
EASI	-45.9 (2.16)	-78.0[f] (1.98)	-87.3[f] (1.98)
SCORAD	-33.6 (1.90)	-61.2[g] (1.70)	-71.0[g] (1.71)
Worst Pruritus NRS	-25.1 (3.35)	-58.1[f] (3.11)	-66.9[f] (3.12)

Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo
[a] Based on number of subjects randomised
[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] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4
[d] N = number of patients whose baseline Worst Pruritus NRS is > 1
[e] % change = least squares mean percent change relative to baseline
[f] multiplicity-controlled p < 0.001 upadacitinib + TCS vs placebo + TCS comparison
[g] nominal p <0.001 upadacitinib + TCS vs placebo + TCS comparison

Figure 8. Proportion of patients achieving an EASI 75 response AD UP Study

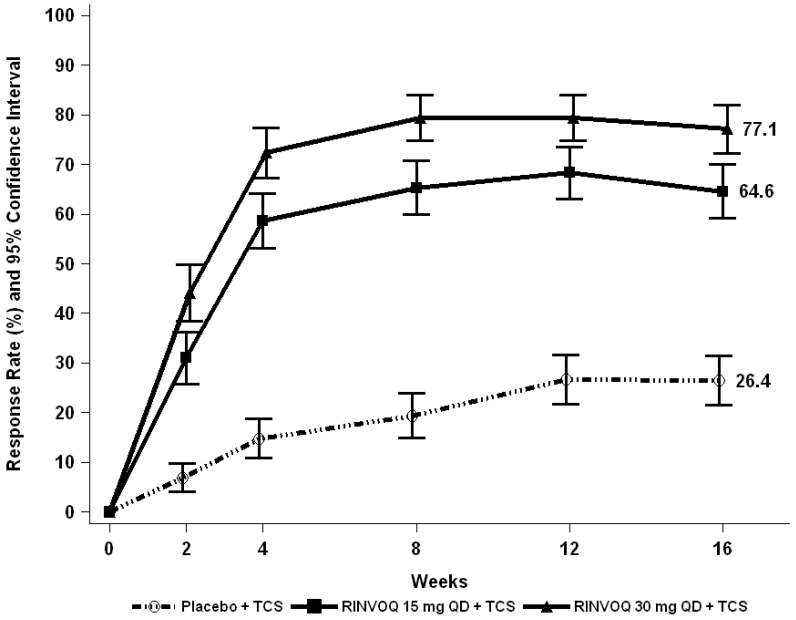
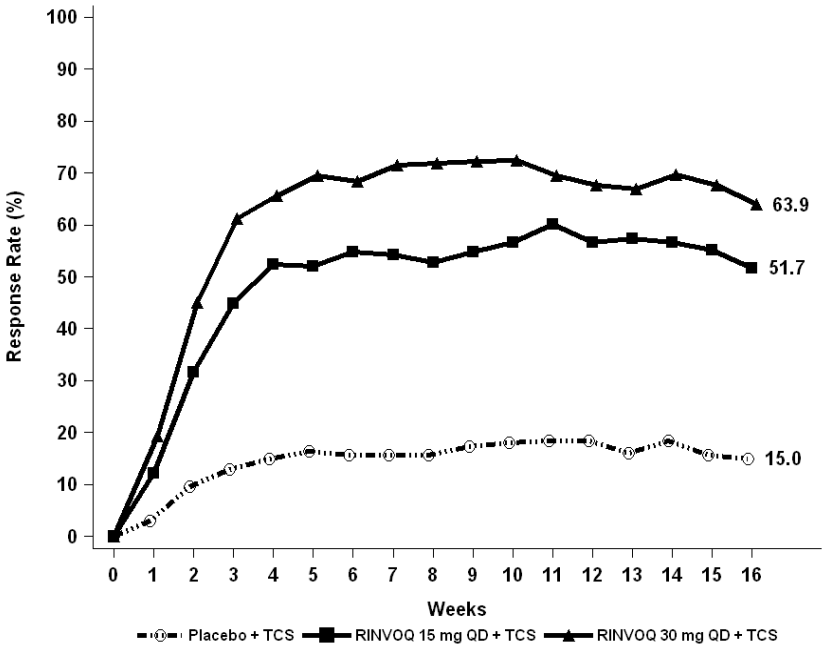


Figure 9. Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in AD UP Study



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.

Subjects treated with either RINVOQ 15 mg or 30 mg had significantly more days free of TCS use with a concurrent EASI 75 response (mean = 33.5 and 47.5 days, respectively) over the 16-week period, compared to placebo group (mean = 7.9 days).

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

Quality of Life/Patient Reported Outcomes

In the MEASURE UP studies, a significantly greater proportion of patients treated with RINVOQ 15 mg or 30 mg reported clinically meaningful reductions in the symptoms of atopic dermatitis and the impact of atopic dermatitis on health-related quality of life compared to placebo at Week 16 (Table 26). A significantly greater proportion of patients treated with RINVOQ achieved clinically meaningful reductions in atopic dermatitis symptom severity as measured by ADerm-SS TSS-7 and ADerm-SS Skin Pain compared to placebo at Week 16. A greater proportion of patients treated with RINVOQ achieved clinically meaningful reductions in the patient-reported effects of atopic dermatitis on sleep, daily activities and emotional state as measured by the ADerm-IS domain scores compared to placebo at Week 16. Similarly, compared to placebo at Week 16, a greater proportion of patients treated with RINVOQ achieved clinically meaningful improvements in atopic dermatitis symptom frequency and health-related quality of life as measured by the POEM and DLQI.

Anxiety and depression symptoms as measured by the HADS score were significantly reduced; in patients with baseline HADS-anxiety or HADS-depression subscale scores ≥ 8 (the cut-off value for anxiety or depression), a greater proportion of patients in the RINVOQ 15 mg or 30 mg groups achieved HADS-anxiety and HADS-depression scores < 8 at Week 16 compared to placebo (Table 28).

Table 28. Patient-reported outcomes results of RINVOQ monotherapy studies at Week 16

Study	MEASURE UP 1			MEASURE UP 2		
Treatment group	PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg
Number of subjects randomised	281	281	285	278	276	282
% responders						
ADerm-SS TSS-7 *(≥ 28-point improvement)* [a,b]	15.0 N=226	53.6 [h] N=233	67.9 [h] N=246	12.7 N=244	53.0[h] N=230	66.2[h] N=234
ADerm-SS Skin Pain *(≥ 4-point improvement)*[a]	15.0 N=233	53.6 [h] N=237	63.5[h] N=249	13.4 N=247	49.4[h] N=237	65.1[h] N=238
ADerm-IS Sleep *(≥ 12-point improvement)* [a,c]	13.2 N=220	55.0[h] N=218	66.1 [h] N=218	12.4 N=233	50.2[h] N=219	62.3[h] N=228
ADerm-IS Daily Activities *(≥ 14-point improvement)* [a,d]	20.3 N=197	65.0 [h] N=203	73.2 [h] N=205	18.9 N=227	57.0[h] N=207	69.5[h] N=223
ADerm-IS Emotional State *(≥ 11-point improvement)* [a,e]	19.8 N=212	62.6 [h] N=227	72.6 [h] N=226	16.7 N=234	57.0[h] N=228	71.5[h] N=228
DLQI *(DLQI 0/1)*[f]	4.4 N=252	30.3[h] N=258	41.5[h] N=261	4.7 N=257	23.8[h] N=252	37.9[h] N=256
DLQI *(≥ 4-point improvement)* [a]	29.0 N=250	75.4[h] N=254	82.0[h] N=256	28.4 N=250	71.7[h] N=251	77.6[h] N=251
POEM *(≥ 4-point improvement)* [a]	22.8 N=276	75.0[h] N=278	81.4[h] N=280	28.7 N=268	70.9[h] N=268	83.5[h] N=269
HADS *(HADS-A < 8 and HADS-D < 8)* [g]	14.3 N=126	45.5[h] N=145	49.2[h] N=144	11.4 N=140	46.0[h] N=137	56.1[h] N=146

Study	MEASURE UP 1	MEASURE UP 2
Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo The threshold values specified correspond to the minimal clinically important difference (MCID) and was used to determine response. [a] N = number of patients whose baseline score is greater than or equal to the MCID. [b] ADerm-SS TSS-7 assesses itch while asleep, itch while awake, skin pain, skin cracking, pain caused by skin cracking, dry skin, and flaking due to AD. [c] ADerm-IS Sleep assesses difficulty falling asleep, sleep impact, and waking up at night due to AD. [d] ADerm-IS Daily Activities assesses AD's effect on household activities, physical activities, social activities, and concentration. [e] ADerm-IS Emotional State assesses self-consciousness, embarrassment, and sadness due to AD. [f] N = number of patients whose baseline DLQI score is > 1. [g] N = number of patients whose baseline HADS-A or HADS-D is ≥ 8. [h] multiplicity-controlled p < 0.001 upadacitinib vs placebo comparison.		

Adolescent Population

A total of 344 adolescents aged 12 to 17 years with moderate-to-severe atopic dermatitis were randomised across the three Phase 3 studies and received 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 29). The adverse event profile in adolescents was generally similar to that in adults. Safety and efficacy of RINVOQ in adolescents weighing less than 40kg and in patients less than 12 years of age with atopic dermatitis have not been established.

Table 29. Efficacy results of RINVOQ for adolescents at Week 16

Study	**MEASURE UP 1**		**MEASURE UP 2**		**AD UP**	
Treatment Group	PBO	UPA 15 mg	PBO	UPA 15 mg	PBO + TCS	UPA 15 mg + TCS
Number of adolescents subjects randomised	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
Worst Pruritus NRS[c] *(≥ 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: UPA= upadacitinib (RINVOQ); PBO = placebo [a] Based on number of subjects randomised [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] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4						

Phase 2b Dose-Ranging Monotherapy Study

RINVOQ 7.5 mg, 15 mg and 30 mg once daily were assessed in a Phase 2b randomised, placebo-controlled, double-blind, dose-ranging, multicenter study (M16-048) of adult patients with moderate to severe atopic dermatitis inadequately controlled by topical medication(s) (Table 30). Based on the results of this study, the 15 mg and 30 mg once daily doses were selected for further investigation in the Phase 3 program.

Table 30. Phase 2b Efficacy Results of RINVOQ at Week 16

Treatment Group	PBO	UPA 7.5 mg	UPA 15 mg	UPA 30 mg
Number of subjects randomised	41	42	42	42
Mean percent change (SE)[a], EASI	-23.0 (6.42)	-39.4 (6.24) [c]	-61.7 (6.12) [e]	-74.4 (6.13) [e]
EASI75, % responders [b]	9.8	28.6 [c]	52.4 [e]	69.0 [e]
Mean percent change (SE)[a], Pruritus NRS	-9.7 (8.30)	-39.6 (8.04) [d]	-48.0 (8.08) [e]	-68.9 (7.79) [e]

Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo; SE= standard error
[a] % change = least squares mean percent change relative to baseline
[b] Based on number of subjects randomised
[c] Nominal p =< 0.05 upadacitinib vs placebo comparison
[d] Nominal p =< 0.01 upadacitinib vs placebo comparison
[e] Nominal p<0.001 upadacitinib vs placebo comparison

Ulcerative Colitis

The efficacy and safety of RINVOQ was evaluated in three multicentre, double-blind, placebo-controlled Phase 3 clinical studies: two replicate induction studies, UC-1 and UC-2, and a maintenance study UC-3. In addition, efficacy and safety of RINVOQ were assessed in long-term extension study, UC-4.

Disease activity was based on the adapted Mayo score (aMS, Mayo scoring system excluding Physician's Global Assessment), which ranged from 0 to 9 and has three subscores that were each scored 0 (normal) to 3 (most severe): stool frequency subscore (SFS), rectal bleeding subscore (RBS), and a centrally-reviewed endoscopy subscore (ES). See Table 31.

Table 31. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
Induction			
U-ACHIEVE Induction (UC-1) **U-ACCOMPLISH (UC-2)**	Biologic failure* (246/473) Without biologic failure† (227/473) Biologic failure (262/515) Without biologic failure (253/515)	• Upadacitinib 45 mg • Placebo	Primary Endpoint: • Clinical remission per Adapted Mayo score at Week 8 Secondary Endpoints at Week 8 or specified: • Endoscopic improvement • Endoscopic remission • Clinical response • Clinical response at Week 2 • Histologic-endoscopic mucosal improvement • No bowel urgency • No abdominal pain • Histologic improvement • Change from baseline in IBDQ total score • Mucosal healing • Change from baseline in FACIT-F score
Maintenance			
U-ACHIEVE Maintenance (UC-3)	Biologic failure (225/451) Without biologic failure (226/451)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Primary Endpoint: • Clinical remission per Adapted Mayo score at Week 52 Secondary Endpoints at Week 52: • Endoscopic improvement • Maintenance of clinical remission • Corticosteroid-free clinical remission • Maintenance of endoscopic improvement • Endoscopic remission • Maintenance of clinical response • Histological-endoscopic mucosal improvement • Change from baseline in IBDQ total • Mucosal healing • No bowel urgency • No abdominal pain • Change from baseline in FACIT-F

*Biologic failure: inadequate response to, loss of response to, or intolerance to prior biologic therapy
†Without biologic failure: inadequate response, loss of response, or intolerance to conventional therapy but had not failed biologic therapy
Abbreviations: IBDQ: inflammatory bowel disease questionnaire, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue score

Induction studies (UC-1 and UC-2)

In studies UC-1 and UC-2, 988 patients (473 and 515 patients, respectively) were randomised to RINVOQ 45 mg once daily or placebo for 8 weeks with a 2:1 treatment allocation ratio and included in the efficacy analysis. All enrolled patients had moderately to severely active ulcerative colitis defined as aMS of 5 to 9 with an ES of 2 or 3 and demonstrated prior treatment failure including inadequate response, loss of response, or intolerance to prior conventional and/or biologic treatment. Prior treatment failure to at least 1 biologic therapy (Prior biologic failure) was seen in 52% (246/473) and 51% (262/515) of patients, respectively. Previous treatment failure to conventional therapy but not biologics (Without prior biologic failure) was seen in 48% (227/473) and 49% (253/515) of patients, respectively.

At baseline in UC-1 and UC-2 respectively, 39% and 37% of patients received corticosteroids, 1.1% and 0.8% of patients received immunomodulators and 68% and 69% of patients received aminosalicylates. Patient disease activity in UC-1 and UC-2 was moderate (aMS ≤7) in 61% of patients and 60% of patients and severe (aMS >7) in 39% and 40% of patients, in respectively.

Results of the primary endpoint of clinical remission at Week 8 and secondary endpoints are listed in Table 32.

Table 32. Proportion of Patients Meeting Primary and Secondary Efficacy Endpoints at Week 8 in Induction Studies UC-1 and UC-2

	UC-1 (U-ACHIEVE)			UC-2 (U-ACCOMPLISH)		
Endpoint	**PBO N=154**	**UPA 45 mg N=319**	**Treatment Difference (95% CI)**	**PBO N=174**	**UPA 45 mg N=341**	**Treatment Difference (95% CI)**
Disease Activity and UC Symptoms						
Clinical remission[a]	4.8%	26.1%	21.6%* (15.8, 27.4)	4.1%	33.5%	29.0%* (23.2, 34.7)
Prior biologic failure+	0.4%	17.9%	17.5%	2.4%	29.6%	27.1%
Without prior biologic failure+	9.2%	35.2%	26.0%	5.9%	37.5%	31.6%
Clinical response[b]	27.3%	72.6%	46.3%* (38.4, 54.2)	25.4%	74.5%	49.4%* (41.7, 57.1)
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%
No bowel urgency	21.4%	48.4%	27.4%* (19.2, 35.6)	25.9%	53.7%	27.1%* (19.0, 35.3)
No abdominal Pain	23.4%	46.6%	23.6%* (15.1, 32.1)	24.1%	53.7%	29.1%* (20.9, 37.4)
Endoscopic and Histologic Assessment						
Endoscopic remission[c]	1.3%	13.7%	12.7%* (8.4, 17.0)	1.7%	18.2%	15.9%* (11.4, 20.3)
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%
Mucosal healing [d]	7.4%	36.3%	29.3%* (22.6, 35.9)	8.3%	44.0%	35.1%* (28.6, 41.6)
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 improvement[e]	22.5%	55.0%	32.2%* (23.8, 40.7)	24.5%	62.2%	37.9%* (29.8, 46.1)
Prior biologic failure+	17.5%	51.0%	33.5%	20.3%	58.3%	38.0%
Without prior biologic failure+	27.6%	59.4%	31.8%	28.8%	66.1%	37.2%
Histologic-endoscopic mucosal healing[f]	6.6%	30.1%	23.7%* (17.5, 30.0)	5.9%	36.7%	30.1%* (24.1, 36.2)
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%

	UC-1 (U-ACHIEVE)			UC-2 (U-ACCOMPLISH)		
Endpoint	**PBO N=154**	**UPA 45 mg N=319**	**Treatment Difference (95% CI)**	**PBO N=174**	**UPA 45 mg N=341**	**Treatment Difference (95% CI)**
Deep mucosal healing[g]	1.3%	10.7%	9.7%* (5.7, 13.7)	1.7%	13.5%	11.3%* (7.2, 15.3)
Prior biologic failure[+]	0	6.5%	6.5%	1.1%	9.2%	8.1%
Without prior biologic failure[+]	2.6%	15.4%	12.8%	2.4%	17.9%	15.5%
Quality of Life						
Change from baseline in FACIT-F score	N = 125 2.8	N = 291 9.5	6.7* (4.79, 8.59)	N = 155 3.5	N = 312 9.4	6.0* (4.19, 7.73)
Change from baseline in IBDQ total score	N = 125 21.7	N = 292 55.3	33.7* (27.02, 40.36)	N = 156 21.1	N = 315 52.2	31.2* (24.98, 37.36)

Abbreviation: PBO = placebo
[+]The number of "Prior biologic failure" patients 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 "Without prior biologic failure" patients 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 aMS: SFS ≤ 1 and not greater than baseline, RBS = 0, ES of ≤ 1 without friability
[b] Per aMS: decrease ≥ 2 points and ≥ 30% from baseline and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤ 1
[c] ES of 0
[d] ES ≤1 without friability (defined as endoscopic improvement in UC-1 and UC-2 protocols).
[e] Decrease from baseline in Geboes score. Histology was assessed using the Geboes score that ranges from 0 to 5.4.
[f] 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 [defined as histologic-endoscopic mucosal improvement in UC-1 and UC-2 protocols]).
[g] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue [defined as mucosal healing in UC-1 and UC-2 protocols])

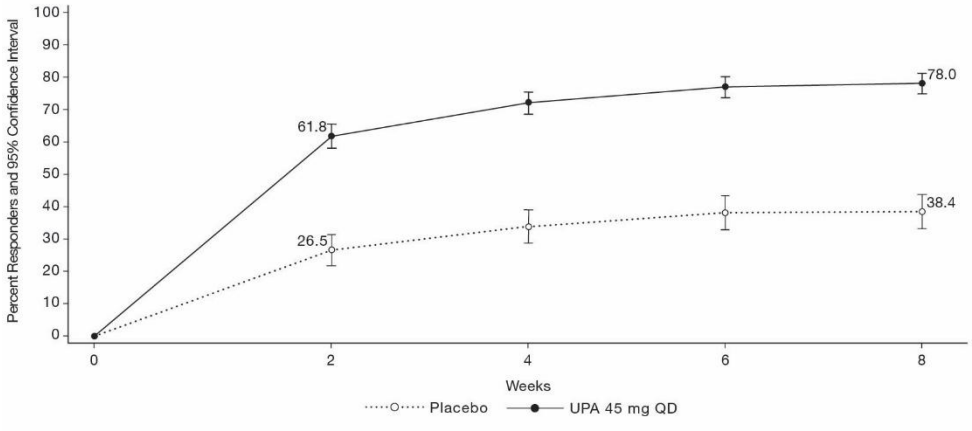
Disease Activity and Symptoms

A significantly greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo had no abdominal pain or no bowel urgency at Week 8 (see Table 32).

For patients with baseline corticosteroid treatment, clinical remission at Week 8 was achieved in 26.5% of patients treated with RINVOQ 45 mg once daily and 4.0% with placebo, and for patients without baseline corticosteroid treatment clinical remission at Week 8 was achieved in 31.9% of patients treated with RINVOQ 45 mg once daily and 4.7% with placebo.

The partial adapted Mayo score (paMS) is composed of SFS and RBS. Clinical response per paMS is defined as a decrease of ≥1 point and ≥30% from baseline and a decrease in RBS ≥1 or an absolute RBS ≤1. The pooled results of clinical response over time per paMS in UC-1 and UC-2 are shown in Figure 10. Onset of efficacy was rapid with a greater proportion of patients treated with RINVOQ 45 mg once daily achieving clinical response as early as Week 2 compared to placebo.

Figure 10. Proportion of patients with clinical response per paMS Over Time in Induction Studies UC-1 and UC-2



Endoscopic and Histologic Assessment

Normalisation of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. At Week 8, a significantly greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo achieved endoscopic remission. Histologic improvement was defined as a decrease from baseline in Geboes score. At Week 8, a significantly greater proportion of patients treated with RINVOQ 45 mg once daily compared to placebo achieved histologic improvement (see Table 30).

Biomarkers of Inflammation

In a pooled analysis of UC-1 and UC-2 at Week 8, high sensitivity CRP (hsCRP) decreased by 6.3 mg/L from baseline (LS mean) in patients treated with RINVOQ 45 mg once daily vs 1.4 mg/L in patients treated with placebo. The rates of fecal calprotectin below 150 mg/kg for RINVOQ 45 once daily were 46.2% compared to 7.8% for placebo.

Quality of Life

Patients treated with RINVOQ 45 mg once daily compared to placebo demonstrated significantly greater and clinically meaningful improvements in health-related quality of life measured by the inflammatory bowel disease questionnaire (IBDQ) and the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F), see Table 30.

Extended Induction

A total of 125 patients in UC-1 and UC-2 who did not achieve clinical response after 8 weeks of treatment with RINVOQ 45 mg once daily entered an 8-week open-label extended induction period. After the treatment of an additional 8 weeks (16 weeks total) of RINVOQ 45 mg once daily, 48.3% of patients achieved clinical response per aMS. Among patients who responded to treatment of 16-week RINVOQ 45 mg once daily, 35.7% and 66.7% of patients maintained clinical response per aMS and 19.0% and 33.3% of patients achieved clinical remission per aMS at Week 52 with maintenance treatment of RINVOQ 15 mg and 30 mg once daily, respectively.

Maintenance Study (UC-3)

The efficacy analysis for UC-3 evaluated 451 patients who achieved clinical response per aMS with 8-week RINVOQ 45 mg once daily induction treatment. Patients were randomised to receive RINVOQ 15 mg, 30 mg or placebo once daily for up to 52 weeks.

The primary endpoint was clinical remission at Week 52. Secondary endpoints are listed in Table 33.

Table 33. Proportion of Patients Meeting Primary and Secondary Efficacy Endpoints at Week 52 in Maintenance Study UC-3

	PBO N=149	UPA 15 mg N=148	UPA 30 mg N=154	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Disease Activity and UC Symptoms					
Clinical remission[a]	12.1%	42.3%	51.7%	30.7%* (21.7, 39.8)	39.0%* (29.7, 48.2)
Prior biologic failure[+]	7.5%	40.5%	49.1%	33.0%	41.6%
Without prior biologic failure[+]	17.6%	43.9%	54.0%	26.3%	36.3%
Maintenance of clinical Remission[b]	N = 54 22.2%	N = 47 59.2%	N = 58 69.7%	37.4%* (20.3, 54.6)	47.0%* (30.7, 63.3)
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[c]	N = 54 22.2%	N = 47 57.1%	N = 58 68.0%	35.4%* (18.2, 52.7)	45.1%* (28.7, 61.6)
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%
Maintenance of clinical response[d]	N = 134 18.8%	N = 135 63.0%	N = 144 76.6%	44.6%* (34.5, 54.7)	56.6%* (47.2, 66.0)
Prior biologic failure	N = 71 15.6%	N = 64 60.9%	N = 66 68.8%	45.4%	53.3%
Without prior biologic failure	N = 63 22.4%	N = 71 64.8%	N = 78 83.2%	42.4%	60.8%
No bowel urgency	17.4%	56.1%	63.6%	38.7%* (28.9, 48.5)	45.1%* (35.5, 54.8)
No abdominal Pain	20.8%	45.9%	55.3%	24.3%* (14.2, 34.5)	33.7%* (23.6, 43.9)
Endoscopic and Histologic Assessment					
Maintenance of mucosal healing[e]	N = 73 19.2%	N = 63 61.6%	N = 79 69.5%	42.0%* (27.8, 56.2)	48.6% (35.5, 61.7)
Prior biologic failure	N = 32 9.4%	N = 24 70.8%	N = 29 60.7%	61.5%	51.3%
Without prior biologic failure	N = 41 26.8%	N = 39 56.0%	N = 50 74.7%	29.2%	47.8%
Endoscopic remission[f]	5.6%	24.2%	25.9%	18.7%* (11.0, 26.4)	19.4%* (11.7, 27.2)
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%

	PBO N=149	UPA 15 mg N=148	UPA 30 mg N=154	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Mucosal healing[g]	14.5%	48.7%	61.6%	34.4%* (25.1, 43.7)	46.3%* (36.7, 55.8)
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 healing[h]	11.9%	35.0%	49.8%	23.8%* (14.8, 32.8)	37.3%* (27.8, 46.8)
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%
Deep mucosal healing[i]	4.7%	17.6%	19.0%	13.0%* (6.0, 20.0)	13.6%* (6.6, 20.6)
Prior biologic failure[+]	2.5%	17.2%	16.1%	14.7%	13.6%
Without prior biologic failure[+]	7.5%	18.0%	21.6%	10.6%	14.2%
Quality of Life					
Change from baseline in FACIT-F score	3.7	8.7	9.5	5.1* (2.67, 7.52)	5.9* (3.44, 8.27)
Change from baseline in IBDQ total score	17.9	49.2	58.9	31.3* (21.98, 40.70)	41.0* (31.39, 50.55)

[+]The number of "Prior biologic failure" patients are 81, 71, and 73 in the placebo, RINVOQ 15 mg, and 30 mg group, respectively. The number of "Without prior biologic failure" patients 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] Per aMS: SFS ≤ 1 and not greater than baseline, RBS = 0, ES of ≤ 1 without friability

[b] Clinical remission per aMS at Week 52 among patients who achieved clinical remission at the end of the induction treatment

[c] Clinical remission per aMS 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.

[d] Clinical response per aMS at Week 52 among patients who achieved clinical response at the end of the induction treatment

[e] Maintain mucosal healing, ES ≤ 1 without friability, among patients with mucosal healing in induction (defined as endoscopic improvement in UC-3 protocol)

[f] ES subscore = 0

[g] ES ≤ 1 without friability (defined as endoscopic improvement in UC-3 protocol)

[h] 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 [defined as histologic-endoscopic mucosal improvement in UC-3 protocol])

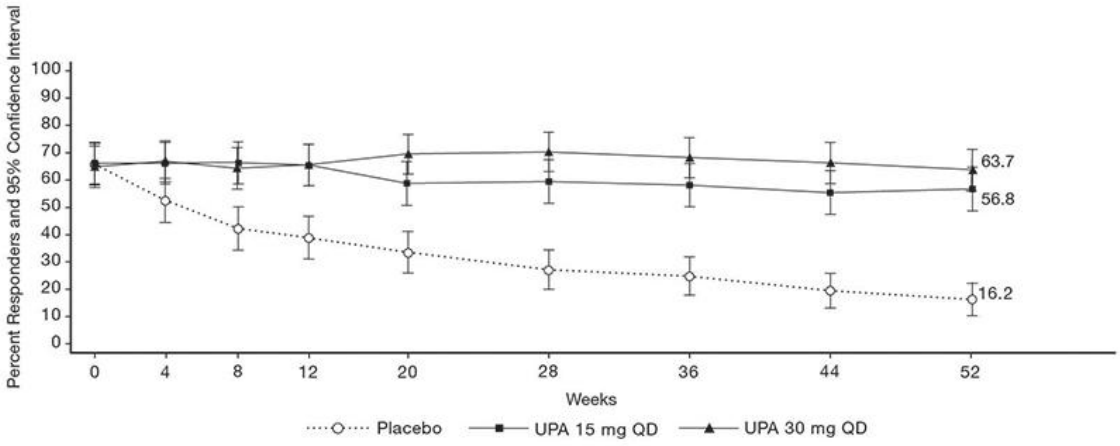
[i] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue [defined as mucosal healing in UC-3 protocol]).

Disease Activity and Symptoms

For patients who achieved clinical remission per aMS at induction, it was maintained at Week 52 by a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo. At Week 52, a greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo had no abdominal pain and no bowel urgency (see Table 33).

Clinical remission, defined as Partial Mayo score (consisting of SFS, RBS and PGA) ≤ 2 with no subscore >1, was achieved over time through Week 52 in more patients treated with both RINVOQ 15 mg and 30 mg once daily compared with placebo (Figure 11).

Figure 11. Proportion of Subjects with Clinical Remission per Partial Mayo Score Over Time in Maintenance Study UC-3.



Endoscopic and Histologic Assessment

In UC-3, a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo achieved endoscopic remission at Week 52. Maintenance of mucosal healing at Week 52 (ES ≤1 without friability) was seen in a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo among patients who achieved mucosal healing at the end of induction (see Table 33).

Histologic improvement (decrease from baseline in Geboes score) was seen in a greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily at Week 52 compared to placebo (42.8% and 56.9% vs 20.6%).

Biomarkers of Inflammation

At Week 52, hsCRP was decreased by 3.9 mg/L and 5.6 mg/L from Baseline (LS mean) in patients treated with RINVOQ 15 mg and 30 mg once daily vs 0.1 mg/L in placebo. The percentage of patients with fecal calprotectin below 150 mg/kg for RINVOQ 15 mg and 30 mg once daily were 43.3% and 46.8%, compared to 12.1% for placebo.

Quality of Life

Patients treated with RINVOQ compared to placebo demonstrated significantly greater and clinically meaningful improvement in health-related quality of life as measured by inflammatory bowel disease questionnaire (IBDQ), Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F). See Table 33.

Long-Term Extension Study (UC-4)

Patients who achieved clinical remission in UC-3 per aMS at 1 year were eligible to continue with the same dose in the extension study (UC-4). After a total of 3 years, 78.6% (55/70) and 84.3% (75/89) of patients maintained clinical remission and 64.7% (22/34) and 74.1% (40/54) of patients maintained endoscopic remission with RINVOQ 15 mg and 30 mg, respectively. Quality of life improvements were also maintained at 3 years. The safety profile of RINVOQ with long-term treatment was consistent with that in the placebo-controlled period.

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.

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.

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.

Table 34. Proportion of Patients Meeting Primary and Secondary 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)**
Disease Activity and CD Symptoms 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)
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)*
Disease Activity and CD Symptoms (early onset)						
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)**
Endoscopic Assessment at Week 12						
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)
Endoscopic remission[f]	2%	19%	17% (12, 22)*	7%	29%	22% (16, 28)*

Abbreviation: PBO = placebo, UPA = upadacitinib
* $p < 0.001$, 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 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 (CDAI or SF/APS) 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

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 34). 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 34). A significantly greater proportion of patients achieved clinical remission at Week 4 compared to placebo (Table 34).

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 34). Improvements were also observed for ulcer-free endoscopy (mucosal healing) in patients treated with RINVOQ 45 mg.

Quality of Life

In CD-1 and CD-2, patients treated with RINVOQ 45 mg demonstrated significantly greater and clinically meaningful improvement from baseline in fatigue, as measured by FACIT-Fatigue score, and health-related quality of life as measured by the 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-randomised 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.

Results of the co-primary endpoints of clinical remission and endoscopic response at Week 52 and secondary endpoints are listed in Table 35.

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Table 35. Proportion of Patients Meeting Primary and Additional Efficacy Endpoints at Week 52 in Maintenance Study CD-3

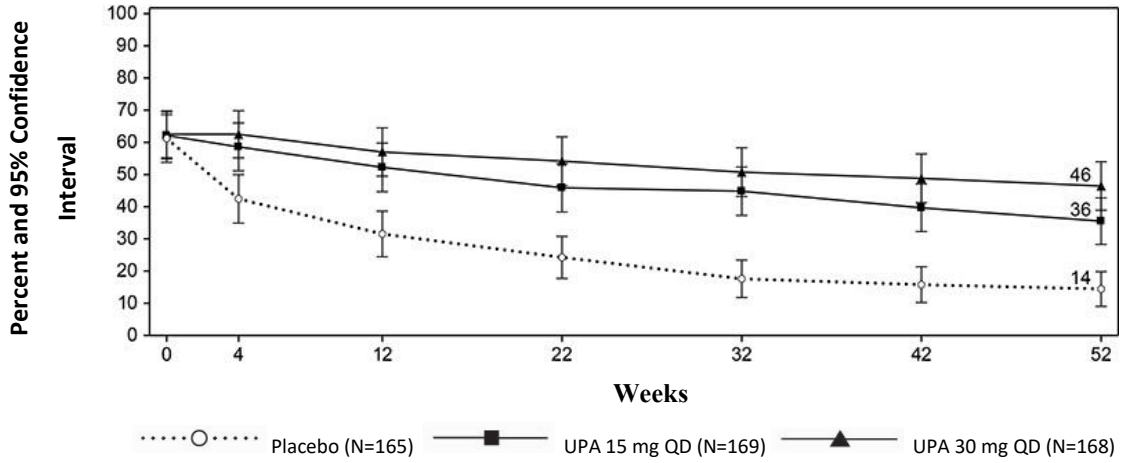
Treatment Group	PBO[+] N=165	UPA 15 mg N=169	UPA 30 mg N=168	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Disease Activity and CD Symptoms					
Clinical remission[a]	14%	36%	46%	22% (14, 30)[*]	32% (23, 40)[*]
Prior biologic failure	N=126 9%	N=124 32%	N=127 43%	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)
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]	14%	35%	45%	21% (13, 30)[*]	30% (21, 39)[*]
Maintenance of clinical remission[a,f]	N=101 20%	N=105 50%	N=105 60%	32% (20, 44)[*]	40% (28, 52)[*]
Endoscopic Assessment					
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)
Endoscopic remission[g]	5%	19%	29%	14% (8, 21)[*]	24% (16, 31)[*]
Deep remission[a,i]	4%	14%	23%	10% (4, 16)[**]	18% (11, 25)[*]

Abbreviation: PBO = placebo, UPA = upadacitinib
[+] 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)
[a] Average daily 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 the subset of patients who were on corticosteroids at induction baseline, 38% (N=63) in RINVOQ 15 mg group, 38% (N=63) in RINVOQ 30 mg group, and 5% (N=61) 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
[i] Clinical remission and endoscopic remission

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 (Figure 12, Table 35).

Figure 12. Proportion of Patients Achieving Clinical Remission in Maintenance Study CD-3



Patients who were not in clinical response per SF/APS to RINVOQ induction at Week 12 in CD-1 and CD-2 (122 patients) received RINVOQ 30 mg once daily for an additional 12 weeks. Of these patients, 53% achieved clinical response at Week 24. Of the patients who responded to the extended treatment period and continued to receive maintenance treatment with RINVOQ 30 mg, 25% achieved clinical remission, and 22% achieved endoscopic response at Week 52.

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 35). Improvements were also observed for ulcer-free endoscopy (mucosal healing) in patients treated with RINVOQ 15 mg and 30 mg.

Resolution of Extra-intestinal Manifestations

Resolution of extra-intestinal manifestations was observed in a significantly greater proportion of patients treated with RINVOQ 30 mg (36%) compared to placebo (15%) at Week 52.

Rescue Treatment

In CD-3, patients who demonstrated inadequate response or lost response during maintenance were eligible to receive rescue treatment with RINVOQ 30 mg. Of the patients who were randomized to RINVOQ 15 mg group and received rescue treatment of RINVOQ 30 mg for at least 12 weeks, 84% achieved clinical response per SF/APS and 48% achieved clinical remission 12 weeks after initiating rescue. Of the patients who were randomized to placebo group and received rescue treatment of RINVOQ 30 mg for at least 12 weeks, 88% achieved clinical response per SF/APS and 53% achieved clinical remission 12 weeks after initiating rescue.

Quality of Life

In CD-3, patients treated with RINVOQ 30 mg demonstrated significantly greater and clinically meaningful 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 health-related quality of life as measured by the inflammatory bowel disease questionnaire (IBDQ), at Week 52 compared to placebo.

5.2 Pharmacokinetic properties

Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once-daily administrations. The pharmacokinetic properties of RINVOQ are provided in Table 36.

Table 36. Pharmacokinetic Properties of RINVOQ

Absorption	
T_{max} (h)	2-4
Effect of high-fat meal (relative to fasting)	No clinically relevant effect AUC: ↑ 29%, C_{max} ↑ 39% to 60%
Distribution	
% Bound to human plasma proteins	59
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism	CYP3A4, CYP2D6 (minor) No active metabolites
Elimination	
Terminal phase elimination $t_{1/2}$ (h)	9-14
% of dose excreted unchanged in urine[a]	24
% of dose excreted unchanged in faeces[a]	38
% of dose excreted as metabolites[a]	34
[a]Based on single dose administration of [^{14}C] upadacitinib immediate-release solution in a mass balance study.	

Pharmacokinetics in special populations

Renal Impairment

Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with stage 2 (estimated GFR [eGFR] of 60-89 mL/min/1.73 m^2), stage 3 (eGFR 30-59 mL/min/1.73 m^2) and stage 4 (eGFR 15-29 mL/min/1.73 m^2) renal impairment, respectively, compared to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). Upadacitinib C_{max} was similar in subjects with normal and impaired renal function. For dosing in patients with renal impairment, see **4.2 Dose and method of administration – Use in Renal Impairment.**

Hepatic Impairment

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC 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).

Other Intrinsic Factors

Age, sex, body weight, race, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure. Upadacitinib pharmacokinetics are consistent across patients with rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, atopic dermatitis, ulcerative colitis and Crohn's disease.

5.3 Preclinical safety data

Upadacitinib is teratogenic in both rats and rabbits (see **4.6 Fertility, Pregnancy and Lactation**)

Genotoxicity

Upadacitinib was not mutagenic in a bacterial mutagenicity assay or clastogenic in an *in vitro* chromosomal aberration assay (human peripheral blood lymphocytes) or an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumourigenicity 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 5 and 12 times the clinical dose of 15 mg, 2 and 6 times the clinical dose of 30 mg and 1.6 and 4 times the clinical dose of 45 mg on an AUC basis for males and females, respectively). No evidence of tumourigenicity was observed in Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day in male or female mice (approximately 3 times the clinical dose of 15 mg, 2 times the clinical dose of 30 mg, and at approximately the same exposure as the clinical dose of 45 mg on an AUC basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 15 mg modified release tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal anhydrous silica, and magnesium stearate. Film coating contains polyvinyl alcohol, macrogol 3350, talc, titanium dioxide, ferrosoferric oxide and iron oxide red.

Each 30 mg modified release tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal anhydrous silica, and

magnesium stearate. Film coating contains polyvinyl alcohol, macrogol 3350, talc, titanium dioxide, and iron oxide red.

Each 45 mg modified release tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal anhydrous silica and magnesium stearate. Film coating contains polyvinyl alcohol, macrogol 3350, talc, titanium dioxide, iron oxide yellow and iron oxide red.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

RINVOQ 15 mg modified release tablets are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side.

RINVOQ 30 mg modified release tablets are red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side.

RINVOQ 45 mg modified release tablets are yellow to mottled yellow, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a45’ on one side.

The following presentations are available:

Starter Pack (7 tablets) - 1 carton containing one PVC/PE/PCTFE/Aluminium blister with 7 tablets.

Monthly Pack (28 tablets) - 1 carton containing four PVC/PE/PCTFE/Aluminium blisters with 7 tablets in each blister. Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Description

Upadacitinib is a white to light brown powder.

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).

Strength equivalency

The strength of upadacitinib is based on anhydrous upadacitinib.

Solubility

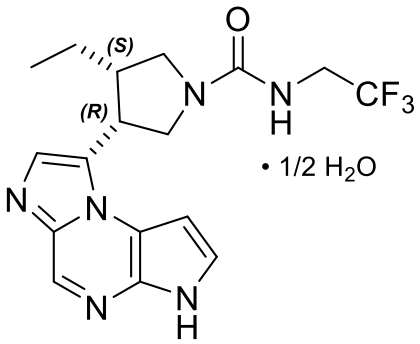
The solubility of upadacitinib in water is 38 to less than 0.2 mg/mL across a pH range of 2 to 9 at 37ºC.

Molecular weight and formula

Upadacitinib has a molecular weight of 389.38 g/mol and a molecular formula of $C_{17}H_{19}F_3N_6O$ • ½ H_2O.

Chemical structure

The chemical structure of upadacitinib is:



CAS number

1310726-60-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine – Schedule 4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

17 January 2020

10 DATE OF REVISION

15 January 2026

Summary table of changes

Section Changed	Summary of new information
4.4 Special warnings and precautions	Addition of retinal vein occlusion
4.8 Adverse Effects	Addition of semen discolouration