NEW ZEALAND DATA SHEET

1 RINVOQ® MODIFIED RELEASE TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rinvoq contains upadacitinib hemihydrate, equivalent to 15 mg, 30 mg or 45 mg of upadacitinib, a 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 adults with moderately to severely active rheumatoid arthritis.

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

Atopic Dermatitis

Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.

Psoriatic arthritis

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

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

Ankylosing spondylitis

Rinvoq is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Non-radiographic Axial Spondyloarthritis

Rinvoq is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.

Giant Cell Arteritis

Rinvoq is indicated for the treatment of adults with giant cell arteritis.

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 biologic agent.

Crohn's Disease

Rinvoq is indicated for the treatment of adult patients with moderately to severely active Crohn’s disease.

4.2 Dose and method of administration

Rinvoq tablets should be taken orally with or without food.

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

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

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 conventional synthetic DMARDs.

Atopic Dermatitis

Adults and adolescent patients 12 years of age and older weighing at least 40 kg

The recommended dose of Rinvoq is 15 mg or 30 mg once daily based on individual patient presentation:

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

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

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

Concomitant Topical Therapies

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

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.

Ankylosing Spondylitis

The recommended dose of Rinvoq is 15 mg once daily.

Non-radiographic Axial Spondyloarthritis

The recommended dose of Rinvoq is 15 mg once daily.

Giant Cell Arteritis

The recommended dose of Rinvoq is 15 mg once daily in combination with a tapering course of corticosteroids. Rinvoq monotherapy should not be used for the treatment of acute relapses (see section 4.4).

Rinvoq 15 mg once daily can be used as monotherapy following discontinuation of corticosteroids. Treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

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. Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance

The recommended maintenance dose of Rinvoq is 15 mg or 30 mg once daily based on individual patient presentation:

- A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment.
- A dose of 30 mg once daily may be appropriate for patients who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose for maintenance should be used.

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

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

Crohn's Disease

Induction

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

Maintenance

The recommended maintenance dose of Rinvoq is 15 mg or 30 mg once daily based on individual patient presentation:

- A dose of 30 mg once daily may be appropriate for patients with high disease burden or those who do not show adequate therapeutic benefit with 15 mg once daily.
- A dose of 30 mg once daily is recommended for patients who have not achieved adequate therapeutic benefit after the initial 12-week induction. For these patients, Rinvoq should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment.
- The lowest effective dose for maintenance should be used.

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

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

Dose Initiation

It is recommended that Rinvoq 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**).

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.

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**).

Table 1. Recommended Dose Interruptions for Laboratory Abnormalities

Laboratory measure	**Action**
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is <1000 cells/mm^3 and may be restarted once ANC return above this value
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is <500 cells/mm^3 and may be restarted once ALC return above this value
Haemoglobin (Hb)	Treatment should be interrupted if Hb is <8 g/dL and may be restarted once Hb return above this value
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Dosing in Special Populations:

Paediatric Use

<u>Atopic Dermatitis</u>

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, 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.

Use in the Elderly

Refer to indication specific guidance.

Use in Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. The use of Rinvoq has not been studied in subjects with end stage renal disease. Haemodialysis is not expected to have a clinically relevant effect on upadacitinib plasma exposures due to the major contribution of non-renal clearance to upadacitinib overall elimination (see **5 PHARMACOLOGICAL PROPERTIES**).

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

Table 2. Recommended Dose for Severe Renal Impairment

	Indication	**Recommended once daily dose**
Severe renal impairment	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, giant cell arteritis, atopic dermatitis, non-radiographic axial spondyloarthritis	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.

4.4 Special warnings and precautions for use

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**). Among opportunistic infections, tuberculosis, multi-dermatomal herpes zoster, oral/oesophageal candidiasis, and cryptococcosis 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.

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.

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

Vaccination

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 and during Rinvoq treatment, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines (see **5 PHARMACOLOGICAL PROPERTIES**).

Malignancy

The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medications may increase the risk of malignancies including lymphoma.

In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of malignancy, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC), was observed with tofacitinib (a different JAK inhibitor) compared to Tumor Necrosis Factor (TNF) blockers. The higher rate of malignancy was primarily observed in patients 65 years of age and older and patients who are current or past long-time smokers.

Malignancies were observed in clinical studies of Rinvoq (see **4.8 ADVERSE EFFECTS**). A higher rate of malignancies, driven by NMSC, was observed with Rinvoq 30 mg compared to Rinvoq 15 mg.

Consider the risks and benefits for the individual patient prior to initiating or continuing therapy with Rinvoq, particularly in patients with current or past malignancy other than successfully treated NMSC, and in individuals who may have an increased risk of malignancies.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with Rinvoq. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Major Adverse Cardiovascular Events (MACE)

In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of MACE, including

myocardial infarction (MI), was observed with tofacitinib (a different JAK inhibitor) compared with TNF blockers. The higher rate of MACE was primarily observed in patients 65 years of age and older, patients with a history of atherosclerotic cardiovascular disease, and patients with other cardiovascular risk factors (such as current or past long-time smokers).

Consider the risks and benefits of Rinvoq treatment prior to initiating therapy in patients with risk factors for cardiovascular disease or when considering continuing Rinvoq in patients who develop MACE. Urgently evaluate and treat patients with signs and symptoms of MACE.

Venous Thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors, including Rinvoq.

In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose-dependent increased incidence of VTE was observed with tofacitinib (a different JAK inhibitor) compared with TNF blockers.

Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use Rinvoq with caution in patients with known risk factors for VTE. Urgently evaluate and treat patients with signs and symptoms of VTE.

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 REACTIONS**).

Gastrointestinal Perforations

Events of gastrointestinal perforations have been reported in clinical trials (*see* **4.8 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 presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Embryo-Foetal Toxicity

Rinvoq may cause foetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception (see **4.6 Fertility, pregnancy, and lactation**).

Immunosuppressive Medicinal Products

Combination with other potent immunosuppressants such as azathioprine, cyclosporine, tacrolimus, and biologic DMARDs or other Janus Kinase (JAK) inhibitors has not been evaluated in clinical studies and is not recommended as a risk of additive immunosuppression cannot be excluded.

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.

Hypoglycaemia in Patients Treated for Diabetes

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

Giant Cell Arteritis

Rinvoq monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established. Corticosteroids should be given according to medical judgement and practice guidelines.

Use in the Elderly

Of the 4381 patients treated in the five rheumatoid arthritis Phase 3 clinical studies, a total of 906 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.

Of the 428 patients treated in the giant cell arteritis Phase 3 clinical study, 350 (81.8%) were 65 years of age or older and 140 (32.7%) were 75 years of age or older.

Of the 2683 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.

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, 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

Neutropenia

Treatment with Rinvoq was associated with an increased incidence of neutropenia (ANC <1000 cells/mm^3). There was no clear association between low neutrophil counts and the occurrence of serious infections.

Lymphopenia

ALCs <500 cells/mm^3 were reported in Rinvoq clinical studies. There was no clear association between low lymphocyte counts and the occurrence of serious infections.

Anaemia

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

The majority of the above haematologic laboratory changes were transient and resolved with temporary treatment interruption.

Evaluate at baseline and thereafter according to routine patient management. Treatment should not be initiated or should be temporarily interrupted in patients who meet the criteria described in Table 1 (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.

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, clarithromycin and grapefruit) (see **5 PHARMACOLOGICAL PROPERTIES**). 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 or 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 and 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), which may lead to reduced therapeutic effect of Rinvoq (see **5 PHARMACOLOGICAL PROPERTIES**). Patients should be monitored for changes in disease activity if Rinvoq is co-administered with strong CYP3A4 inducers.

Potential for Other Medicines to Affect the Pharmacokinetics of Upadacitinib

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

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

				Ratio (90% CI)[a]		
Co-administered Medicine	**Regimen of Co-administered Medicine**	**Regimen of Upadacitinib**	**N**	**C_{max}**	**AUC**	**Clinical Impact**
Ketoconazole	400 mg once daily x 6 days	3 mg single dose[b]	11	1.70 (1.55-1.89)	1.75 (1.62-1.88)	Rinvoq 15 mg once daily is the recommended dose for rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, giant cell arteritis and atopic dermatitis. Use with caution if used chronically. For ulcerative colitis and Crohn's disease, the induction dose should be reduced to 30 mg and the maintenance dose should be reduced to 15 mg when combined with strong CYP3A4 inhibitors.
Rifampicin	600 mg once daily x 9 days	12 mg single dose[b]	12	0.49 (0.44-0.55)	0.39 (0.37-0.42)	May decrease efficacy

CI: Confidence interval
[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.
[b] Upadacitinib was administered as an immediate-release formulation.

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 Medicines

The effect of upadacitinib on plasma exposures of other medicines is provided in Table 4.

Table 4. Change in Pharmacokinetics of Co-administered Medicines in the Presence of Upadacitinib

				Ratio (90% CI)[a]		
Co-administered Medicine	**Regimen of Co-administered Medicine**	**Regimen of Upadacitinib**	**N**	**C_{max}**	**AUC**	**Clinical Impact**
Midazolam	5 mg single dose	30 mg once daily x 10 days	20	0.74 (0.68-0.80)	0.74 (0.68-0.80)	No dose adjustment
Midazolam	5 mg single dose	45 mg once daily x 10 days	19	0.75 (0.69-0.83)	0.76 (0.69-0.83)	No dose adjustment
Dextromethorphan	30 mg single dose	45 mg once daily x 11 days	19	1.30 (1.13-1.50)	1.35 (1.18-1.54)	No dose adjustment
Rosuvastatin	5 mg single dose	30 mg once daily x 10 days	12	0.77 (0.63-0.94)	0.67 (0.56-0.82)	No dose adjustment
Atorvastatin	10 mg single dose	30 mg once daily x 10 days	24	0.88 (0.79-0.97)	0.77 (0.70-0.85)	No dose adjustment

CI: Confidence interval

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

Upadacitinib has no relevant effects on plasma exposures of ethinyloestradiol, levonorgestrel, methotrexate, or medicines that are substrates for metabolism by CYP1A2, CYP2B6, CYP2C19, or CYP2C9.

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. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study were attributed to the developmental/teratogenic effects of upadacitinib in rats.

Use in Pregnancy (Pregnancy Category D)

The limited human data with Rinvoq in pregnant women are not sufficient to inform drug-associated risk for major birth defects and miscarriage.

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

Based on animal studies, upadacitinib has the potential to affect a developing foetus.

In animal embryo-foetal development studies, upadacitinib was teratogenic in rats and rabbits when pregnant animals received upadacitinib during the period of organogenesis at exposure multiples of 1.6 and 15 times the clinical dose of 15 mg, 0.8 and 7.6 times the clinical dose of 30 mg, and 0.6 and 6 times the clinical dose of 45 mg for rats and rabbits, respectively (see Animal Data). Further, in a pre-/postnatal development study in rats, upadacitinib administration resulted in no drug-related effects in the mothers or pups.

Animal Data

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

In two rat embryo-foetal development studies, pregnant animals were dosed during the period of organogenesis from gestation day (GD) 6 to GD 17. Upadacitinib was teratogenic at all dose levels studied in rats except the lowest dose of 1.5 mg/kg/day. At doses of 4, 5, 25, and 75 mg/kg/day, upadacitinib-related effects included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and, at 75 mg/kg/day, an increase in bent bones of the fore- and hind-limbs. Additionally, at 25 and 75 mg/kg/day, there was an increase in bent ribs, a skeletal variation, which was also considered upadacitinib-related.

In a rabbit embryo-foetal development study, pregnant animals were dosed during the period of organogenesis from GD 7 to GD 19. Upadacitinib was teratogenic when given at doses of 25 mg/kg/day. Developmental effects observed at 25 mg/kg/day in rabbits included an increase in post-implantation losses, increase in total and early resorptions, lower foetal body weights, and increased incidence of cardiac malformations. In addition, maternal toxicity was evident within the 25 mg/kg/day dose group as weight loss, lower food consumption, and the increased occurrence of aborted pregnancies.

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

Use in Lactation

It is unknown whether upadacitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk.

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

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.

4.7 Effects on ability to drive and use machines

Rinvoq has no or negligible influence on the ability to drive and use machines.

4.8 Adverse effects (Undesirable effects)

Clinical trials experience

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 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 comparison to placebo for up to 12-14 weeks after treatment initiation.

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.

Table 5. Adverse Drug Reactions

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)*		Pneumonia Herpes zoster Herpes simplex** Oral candidiasis
Blood and lymphatic system disorders		Neutropenia	
Metabolism and nutrition disorders		Hypercholesterolaemia	Hypertriglyceridemia
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea	
General disorders and administration site conditions		Pyrexia	
Investigations		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.

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 15 mg, 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

Rinvoq 15 mg treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled studies, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with Rinvoq 15 mg are summarised below:

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

Creatinine 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 and then remained stable at the 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.

Atopic Dermatitis

Tabulated summary of adverse reactions

A total of 2893 patients with atopic dermatitis were treated with Rinvoq 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.

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.

Table 6. Adverse Drug Reactions

System Organ Class	Very Common	Common	Uncommon
Infections and Infestations	Upper respiratory tract infections (URTI)[a]	Herpes simplex[b] Herpes zoster Folliculitis influenza	Pneumonia Oral candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancer[d]
Blood and lymphatic system disorders		Neutropenia Anaemia	
Metabolism and nutrition disorders			Hypercholesterolemia Hypertriglyceridemia
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea Abdominal pain[c]	
General disorders and administration site conditions		Pyrexia Fatigue	
Investigations		Blood creatine phosphokinase increased Weight increased	ALT increased AST increased
Skin and subcutaneous tissue disorders	Acne	Urticaria	
Nervous system disorders		Headache	

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

[b] Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes

[c] Includes abdominal pain and abdominal pain upper

[d] Presented as a group 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 TB and herpes zoster) reported in the global AD 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.

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 events 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 AD 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 15 mg, 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 treatment was associated with dose-related increases in lipid parameters including total cholesterol, LDL cholesterol, and HDL cholesterol. In controlled studies, for up to 16 weeks, changes from baseline in lipid parameters are summarised below:

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

Small increases in LDL cholesterol were observed after Week 16.

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, hemoglobin 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 sub-studies (n=198), of whom 264 were exposed to 15 mg and 265 were exposed to 30 mg. The safety profile for Rinvoq 15 mg and 30 mg was similar in adolescents and adults. With long-term exposure, the adverse reaction of skin papilloma was reported in 3.4% and 6.8% of adolescents with atopic dermatitis in the Rinvoq 15 mg and 30 mg groups, respectively.

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

Overall, the safety profile observed in patients with active non-radiographic axial spondyloarthritis treated with Rinvoq 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. 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 577.3 patient-years of exposure, of whom 228 were exposed to Rinvoq 15 mg for at least one year.

Overall, the safety profile observed in patients with active ankylosing spondylitis treated with Rinvoq 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. No new safety findings were identified.

Giant Cell Arteritis

In the Phase 3 study, 209 patients with giant cell arteritis received at least 1 dose of Rinvoq 15 mg, of whom 122 were exposed for at least one year during the 52-week placebo-controlled period.

The safety profile observed in patients with giant cell arteritis was generally consistent with the safety profile observed in patients with rheumatoid arthritis. During the 52-week placebo-controlled period, peripheral oedema was identified as an adverse drug reaction with the incidence rate of 8.6% in patients treated with Rinvoq 15 mg and a 26-week corticosteroid taper compared to 2.7% in patients treated with placebo and a 52-week corticosteroid taper. A higher incidence of headache was also observed in patients treated with Rinvoq 15 mg (16.3%) compared to placebo (11.6%).

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 **PHARMACODYNAMIC PROPERTIES: Ulcerative Colitis**) with a total of 1313 patients representing 3537 patient-years of exposure, of whom a total of 929 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.

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.

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.

Table 7. Adverse Drug Reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)[a]	Herpes zoster[a] Herpes simplex[a] Folliculitis Influenza	Pneumonia[a]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancer[a]	
Blood and lymphatic system disorders		Neutropaenia[a] Lymphopaenia[a]	
Metabolism and nutrition disorders		Hypercholesterolaemia[a] Hyperlipidaemia[a]	
Skin and subcutaneous tissue disorders		Acne[a] Rash[a]	
General disorders and administration site conditions		Pyrexia	
Investigations		Blood CPK increased ALT increased AST increased	
[a] 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 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 per 100 patient-years, respectively.

Herpes zoster was reported in 0 patients treated with placebo and 4 patients (3.8 per 100 patient-years) treated with Rinvoq 45 mg through 8 weeks. In patients who received Rinvoq 45 mg induction treatment for up to 16 weeks in UC-1 and UC-2, herpes zoster was reported in 5 patients (12.9 per 100 patient-years). 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 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 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:

- Mean total cholesterol increased by 0.95 mmol/L in the Rinvoq 45 mg induction group and by 0.87 mmol/L and 1.19 mmol/L in the Rinvoq 15 mg and 30 mg maintenance groups, respectively.
- Mean HDL increased by 0.44 mmol/L in the Rinvoq 45 mg induction group and by 0.24 mmol/L and 0.34 mmol/L in the Rinvoq 15 mg and 30 mg maintenance groups, respectively.
- Mean LDL increased by 0.52 mmol/L in the Rinvoq 45 mg induction group and by 0.64 mmol/L and 0.80 mmol/L in the Rinvoq 15 mg and 30 mg maintenance groups, respectively.
- Mean triglycerides decreased by 0.05 mmol/L in the Rinvoq 45 mg induction group and changed by 0.02 mmol/L and 0.12 mmol/L in the Rinvoq 15 mg and 30 mg maintenance 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 0.8% 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 1.2% 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, haemoglobin 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, haemoglobin decreases below 8 g/dL in at least one measurement occurred in 0% 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 representing 1203 patient-years of exposure, of whom a total of 536 patients were exposed for at least one year.

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

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

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

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.

Table 8. Adverse Drug Reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)[a]	Bronchitis[a] Herpes zoster[a] Herpes simplex[a] Folliculitis Influenza Pneumonia[a]	Oral candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancer[a]
Blood and lymphatic system disorders		Anaemia[a] Neutropaenia[a]	
Metabolism and nutrition disorders		Hypercholesterolaemia[a] Hyperlipidaemia[a]	
Skin and subcutaneous tissue disorders		Acne[a]	
General disorders and administration site conditions		Fatigue Pyrexia	
Investigations		Blood CPK increased ALT increased AST increased	
Nervous system disorders		Headache[a]	
[a] Presented as grouped term			

Specific Adverse Reactions

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 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.

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

Reproductive system and breast disorders: Semen discolouration

Reports of semen discolouration (blue or green) have occurred in patients taking Rinvoq. Most reports occurred in patients taking Rinvoq for ulcerative colitis or Crohn's disease during the induction phase with 45 mg. 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. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

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 risk assessment and advice on the management of overdose in New Zealand, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

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 50–70-fold greater selectivity for JAK1 over JAK2 and >100-fold 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 signalling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus. Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15 and IFNγ) transduce signals via the JAK1 pathway and are involved in pathology of inflammatory bowel diseases. JAK1 inhibition with upadacitinib modulates the signaling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of inflammatory bowel diseases.

Pharmacodynamics

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

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

Lymphocytes

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

Immunoglobulins

In patients with rheumatoid arthritis, small decreases from baseline in mean IgG and IgM levels were observed with upadacitinib treatment in the controlled period; 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 faecal 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.

Vaccine Studies

The influence of Rinvoq on the humoral response following administration of adjuvanted recombinant glycoprotein E herpes zoster 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, 4 weeks post vaccination dose 2, 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. Vaccination resulted in 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.

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 9). 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 up to 10 years.

Table 9. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT EARLY	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 • SF-36 PCS
SELECT MONOTHERAPY	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 • SF-36 PCS • Morning stiffness
SELECT NEXT	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 • SF-36 PCS • Morning stiffness • FACIT-F
SELECT COMPARE	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) at Week 12 • Radiographic progression (ΔmTSS) at Week 26 • SF-36 PCS

			• Morning stiffness • FACIT-F
SELECT BEYOND	bDMARD-IR[e] (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoint: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS

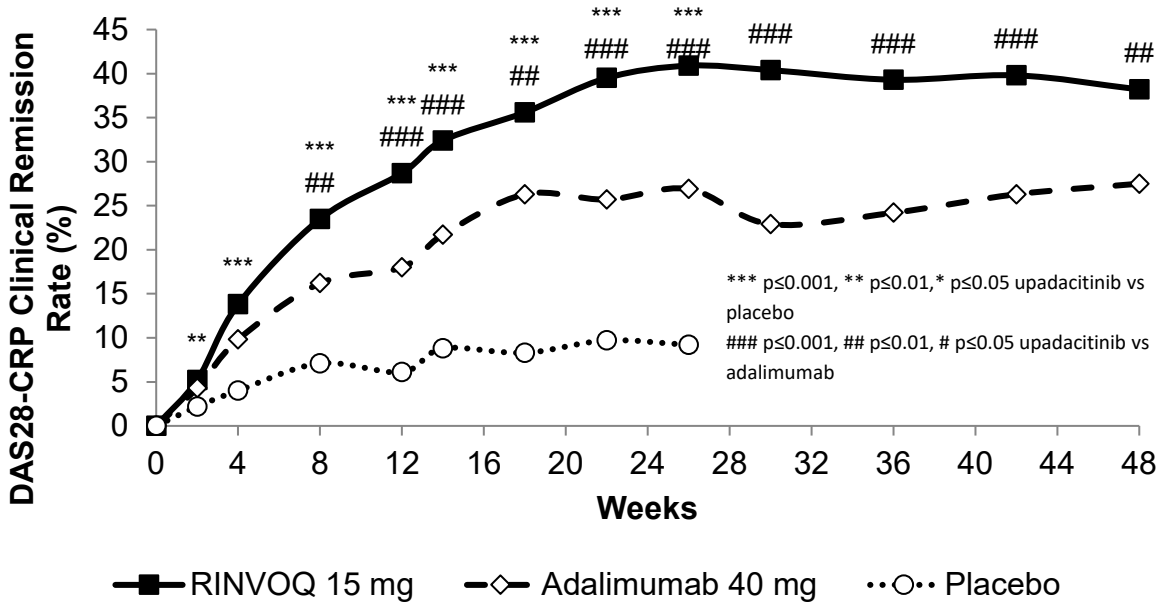
Abbreviations:
ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement
bDMARD = biologic disease-modifying anti-rheumatic drug
CR = Clinical Response
CRP = C-Reactive Protein
DAS28 = Disease Activity Score 28 joints
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue
mTSS = modified Total Sharp Score
csDMARD = conventional synthetic disease-modifying anti-rheumatic drug
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

Remission and low disease activity

In all studies, a significantly higher proportion of patients treated with Rinvoq 15 mg achieved both low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX, or adalimumab (Table 10). Compared to adalimumab, significantly higher responses were achieved as early as Week 8 and maintained through Week 48 (Figure 1). Significantly higher responses were also observed for other disease activity outcomes including CDAI ≤2.8, SDAI ≤3.3, and Boolean remission. 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.

Figure 1. Clinical Remission (DAS28-CRP) over time in SELECT COMPARE



ACR Response

In all studies, significantly more patients treated with Rinvoq 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo or MTX except for ACR70 in SELECT-BEYOND (Table 10). Time to onset of efficacy was rapid across measures with significantly 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. The percentage of patients who achieved ACR20/50/70 responses at each visit in SELECT-COMPARE are shown in Figure 2, Figure 3 and Figure 4.

Treatment with Rinvoq 15 mg, alone or in combination with csDMARDs, resulted in significant 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 (Table 11).

In SELECT-COMPARE, a significantly higher proportion of patients treated with Rinvoq 15 mg achieved ACR20/50/70 at Weeks 12 through 48 compared to adalimumab. In addition, greater improvements were observed for individual ACR components (Table 11).

Figure 2. Percent of Patients Achieving ACR20 in SELECT COMPARE

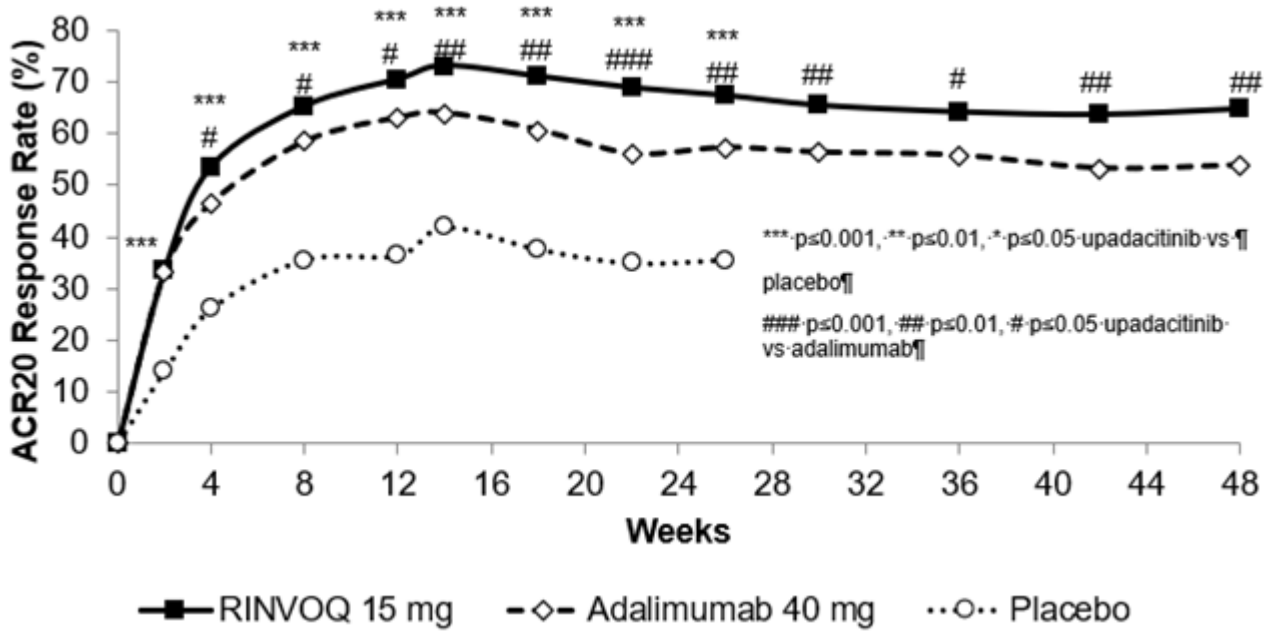


Figure 3. Percent of Patients Achieving ACR50 in SELECT COMPARE

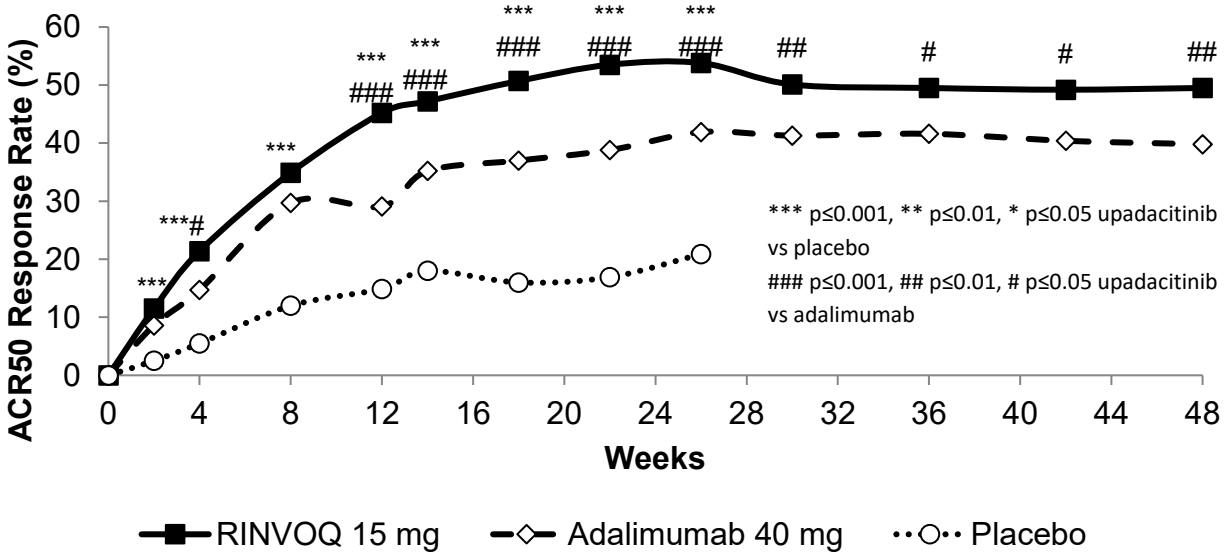


Figure 4. Percent of Patients Achieving ACR70 in SELECT COMPARE

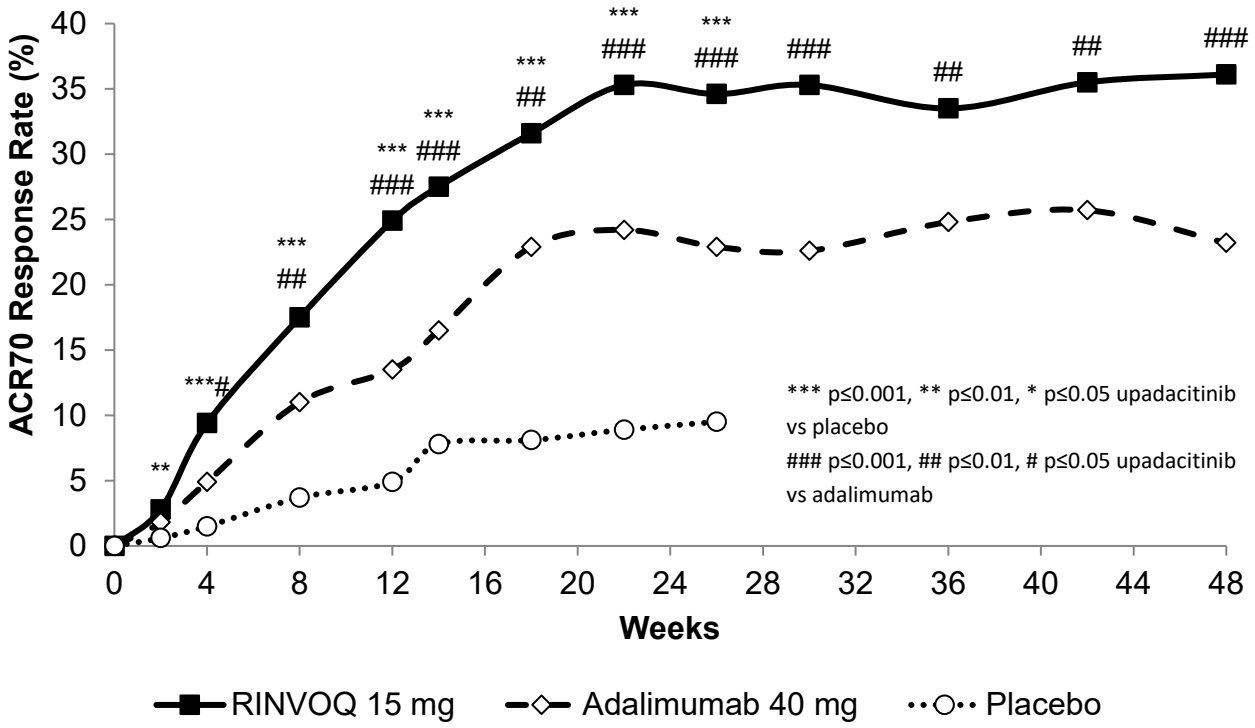


Table 10. Response and Remission

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[e]	41	68[e]	36	64[e]	36	71[e,j]	63	28	65[e]
24[c]/26[d]	59	79[e]					36	67[e,i]	57		
48	57	74[e]						65[j]	54		
ACR50 (% of patients)											
12[a]/14[b]	28	52[e]	15	42[e]	15	38[e]	15	45[e,h]	29	12	34[e]
24[c]/26[d]	33	60[e]					21	54[e,h]	42		
48	43	63[e]						49[j]	40		
ACR70 (% of patients)											
12[a]/14[b]	14	32[e]	3	23[e]	6	21[e]	5	25[e,h]	13	7	12
24[c]/26[d]	18	44[e]					10	35[e,h]	23		
48	29	51[e]						36[h]	23		
LDA DAS28-CRP ≤3.2 (% of patients)											
12[a]/14[b]	28	53[e]	19	45[e]	17	48[e]	14	45[e,h]	29	14	43[e]
24[c]/26[d]	32	60[e]					18	55[e,h]	39		
48	39	59[e]						50[h]	35		

Study	SELECT EARLY MTX-Naïve		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND bDMARD-IR	
CR DAS28-CRP <2.6 (% of patients)											
12[a]/14[b]	14	36[e]	8	28[e]	10	31[e]	6	29[e,h]	18	9	29[e]
24[c]/26[d]	18	48[e]					9	41[e,h]	27		
48	29	49[e]						38[i]	28		
SDAI ≤3.3 (% of patients)											
12[a]/14[b]	6	16[e]	1	14[e]	3	10[f]	3	12[e,j]	7	5	9
24[c]/26[d]	9	28[e]					5	24[e,h]	14		
48	16	32[e]						25[i]	17		
CDAI ≤2.8 (% of patients)											
12[a]/14[b]	6	16[e]	1	13[e]	3	9[f]	3	13[e,i]	8	5	8
24[c]/26[d]	11	28[e]					6	23[e,h]	14		
48	17	32[e]						25[i]	17		
Boolean Remission (% of patients)											
12[a]/14[b]	6	13[f]	1	9[e]	4	10[f]	2	10[e,i]	4	2	7[g]
24[c]/26[d]	7	24[e]					4	18[e,h]	10		
48	13	28[e]						21[j]	15		

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, csDMARD = conventional synthetic disease modifying anti-rheumatic drug; 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] p≤0.001 upadacitinib vs placebo or MTX comparison

[f] p≤0.01 upadacitinib vs placebo or MTX comparison

[g] p<0.05 upadacitinib vs placebo or MTX comparison

[h] p≤0.001 upadacitinib vs adalimumab comparison

[i] p≤0.01 upadacitinib vs adalimumab comparison

[j] p<0.05 upadacitinib vs adalimumab comparison

Table 11. Components of ACR Response (mean change from baseline)[a]

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											
Number of tender joints (0-68)											
12[b]/14[c]	-13	-17[h]	-11	-15[h]	-8	-14[h]	-10	-16[h,k]	-14	-8	-16[h]
24[d]/26[e]	-16	-19[h]					-9	-18[h,j]	-15		
Number of swollen joints (0-66)											
12[b]/14[c]	-10	-12[h]	-8	-11[h]	-6	-9[h]	-7	-11[h]	-10	-6	-11[h]
24[d]/26[e]	-12	-14					-6	-12[h]	-11		
Pain[f]											
12[b]/14[c]	-25	-36[h]	-14	-26[h]	-10	-30[h]	-15	-32[h,i]	-25	-10	-26[h]
24[d]/26[e]	-28	-40[h]					-19	-37[hj]	-32		
Patient global assessment[f]											
12[b]/14[c]	-25	-35[h]	-11	-23[h]	-10	-30[h]	-15	-30[h,i]	-24	-10	-26[h]
24[d]/26[e]	-28	-39[h]					-18	-36[h,j]	-30		
Disability Index (HAQ-DI)[g]											
12[b]/14[c]	-0.5	-0.8[h]	-0.3	-0.7[h]	-0.3	-0.6[h]	-0.3	-0.6[h,j]	-0.5	-0.2	-0.4[h]
24[d]/26[e]	-0.6	-0.9[h]					-0.3	-0.7[h,j]	-0.6		
Physician global assessment[f]											
12[b]/14[c]	-35	-46[h]	-26	-40[h]	-23	-38[h]	-25	-39[h]	-36	-26	-39[h]
24[d]/26[e]	-45	-50[h]					-27	-45[h,j]	-41		
hsCRP (mg/L)											
12[b]/14[c]	-10.6	-17.5[h]	-1.1	-10.2[h]	-0.4	-10.1[h]	-1.7	-12.5[h,j]	-9.2	-1.1	-11.0[h]
24[d]/26[e]	-11.6	-18.4[h]					-1.5	-13.5[h,j]	-10.3		

Abbreviations:
ACR = American College of Rheumatology
ADA = adalimumab
bDMARD = biologic disease-modifying anti rheumatic drug
hsCRP = high-sensitivity c-reactive protein
csDMARD = conventional synthetic disease-modifying anti-rheumatic drug
HAQ-DI = Health Assessment Questionnaire Disability Index
IR = inadequate responder
MTX = methotrexate
PBO = placebo
UPA = upadacitinib
[a] Data shown are mean
[b] SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND
[c] SELECT-MONOTHERAPY
[d] SELECT-EARLY
[e] SELECT-COMPARE
[f] Visual analog scale: 0 = best, 100 = worst
[g] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[h] p≤0.001 upadacitinib vs placebo or MTX comparison
[i] p≤0.001 upadacitinib vs adalimumab comparison
[j] p≤0.01 upadacitinib vs adalimumab comparison
[k] 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 12). 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) 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 12. Radiographic Changes

Study	**SELECT EARLY MTX-Naïve**		**SELECT COMPARE MTX-IR**		
Treatment Group	MTX	UPA 15 mg	PBO[a]	UPA 15 mg	ADA 40 mg
Modified Total Sharps Score, mean change from baseline					
Week 24[b]/26[c]	0.7	0.1[f]	0.9	0.2[e]	0.1
Week 48			1.7	0.3[e]	0.4
Erosion Score, mean change from baseline					
Week 24[b]/26[c]	0.3	0.1[e]	0.4	0[e]	0
Week 48			0.8	0.1[e]	0.2
Joint Space Narrowing Score, mean change from baseline					
Week 24[b]/26[c]	0.3	0.1[g]	0.6	0.2[e]	0.1
Week 48			0.8	0.2[e]	0.2
Proportion of patients with no radiographic progression[d]					
Week 24[b]/26[c]	77.7	87.5[f]	76.0	83.5[f]	86.8
Week 48			74.1	86.4[e]	87.9

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

Physical Function Response and Health-Related Outcomes

Treatment with Rinvoq 15 mg, alone or in combination with csDMARDs, resulted in a significant improvement in physical function compared to all comparators (placebo, MTX, adalimumab) as measured by HAQ-DI. Improvements were seen as early as Week 1 compared to placebo in SELECT-NEXT and SELECT-BEYOND and were maintained for up to 60 weeks. In SELECT-COMPARE, patients treated with Rinvoq 15 mg had significantly greater improvement in physical function compared to adalimumab as early as Week 8 and maintained through Week 48.

In all studies, treatment with Rinvoq 15 mg, alone or in combination with csDMARDs, resulted in a significantly greater improvement in pain compared to all comparators, as measured on a 0-100 visual analogue scale, at 12/14 weeks, with responses maintained for up to 48-60 weeks. Significantly greater pain reduction was seen as early as Week 1 compared to placebo and as early as Week 4 compared to adalimumab.

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.

In all studies, treatment with Rinvoq 15 mg resulted in a significantly greater improvement in the mean duration and severity of morning joint stiffness compared to placebo or MTX. In SELECT-COMPARE, patients treated with Rinvoq 15 mg had significantly greater improvement in severity of morning joint stiffness compared to adalimumab.

Across all studies, patients receiving Rinvoq 15 mg experienced significantly greater improvement from baseline in physical component summary (PCS) score of the Short Form Health Survey (SF-36) compared to placebo, adalimumab, or MTX. In SELECT-EARLY, SELECT-MONOTHERAPY, and SELECT-COMPARE patients receiving Rinvoq 15 mg experienced significantly greater improvement from baseline in mental component summary (MCS) scores and in all 8 domains of SF-36 compared to placebo or MTX.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in SELECT-EARLY, SELECT-NEXT, SELECT-EARLY and SELECT- COMPARE studies. Treatment with Rinvoq 15 mg resulted in significant improvement in fatigue compared to placebo, MTX, or adalimumab.

RA-associated work instability was assessed by the Rheumatoid Arthritis-Work Instability Scale (RA-WIS) in employed patients in SELECT-NEXT and SELECT-COMPARE. Treatment with Rinvoq 15 mg resulted in significantly greater reduction in work instability compared to placebo.

Atopic Dermatitis

The efficacy and safety of Rinvoq 15 mg and 30 mg once daily were assessed in three Phase 3 randomised, double-blind, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 2782 patients (12 years of age and older) (Table 13). Rinvoq was evaluated in 542 adolescent (344 in the primary analysis) and 2240 adult patients with moderate to severe atopic dermatitis (AD) 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 AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 (composite score assessing extent and severity of erythema, edema/papulation, scratches and lichenification across 4 different body sites), a minimum body surface area (BSA) involvement of ≥10%, and weekly average Worst Pruritus Numerical Rating Scale (NRS) ≥4.

In all three studies, patients received Rinvoq once daily 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 13. 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 (30 mg), Day 3 (15 mg) • % 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

Study Name	Treatment Arms	Key Outcome Measures
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 (30 mg) • % 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 14). 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 5 and Figure 6 show 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.

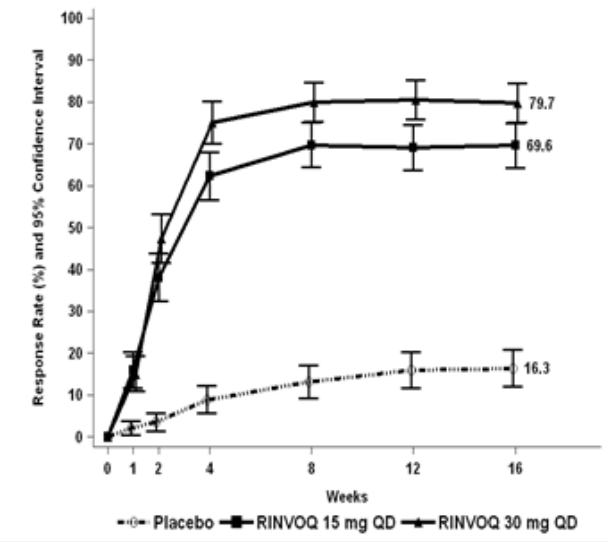
Table 14. Efficacy Results of Rinvoq Monotherapy Studies at Week 16

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

MEASURE UP 1 **MEASURE UP 2**



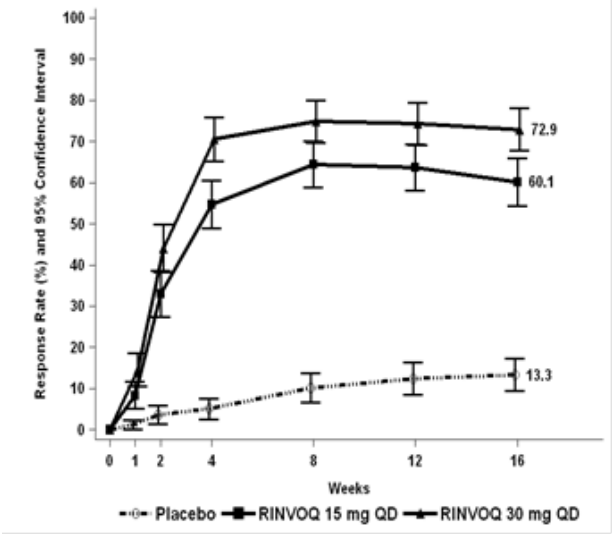
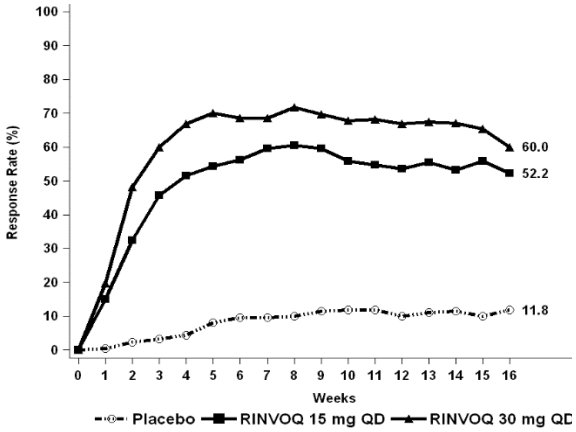
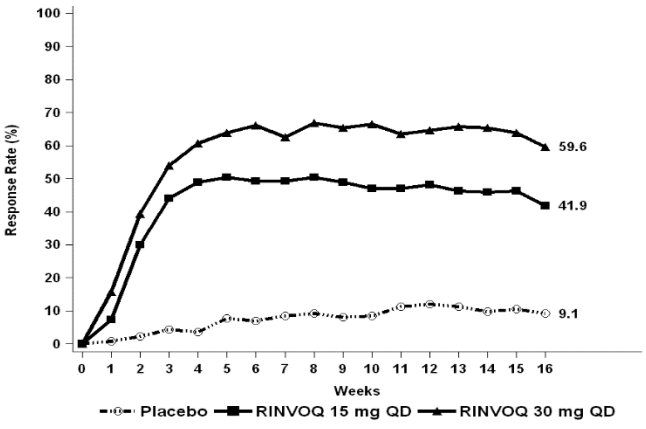


Figure 6. Proportion of patients with ≥4-point improvement in the Worst Pruritis NRS in monotherapy studies

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 15). 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 7 and Figure 8 show 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 15. 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 <0.001upadacitinib + TCS vs placebo + TCS comparison

Figure 7. Proportion of patients achieving an EASI 75 response AD UP Study

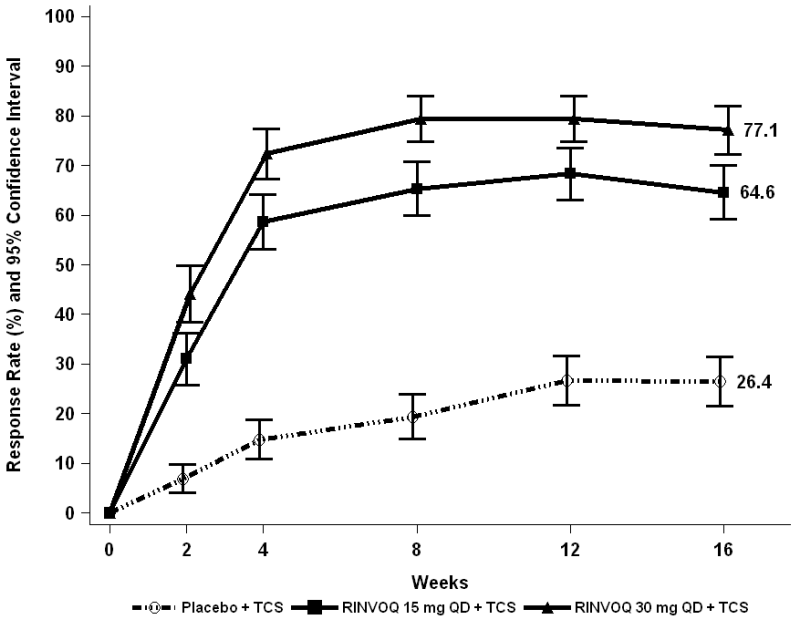
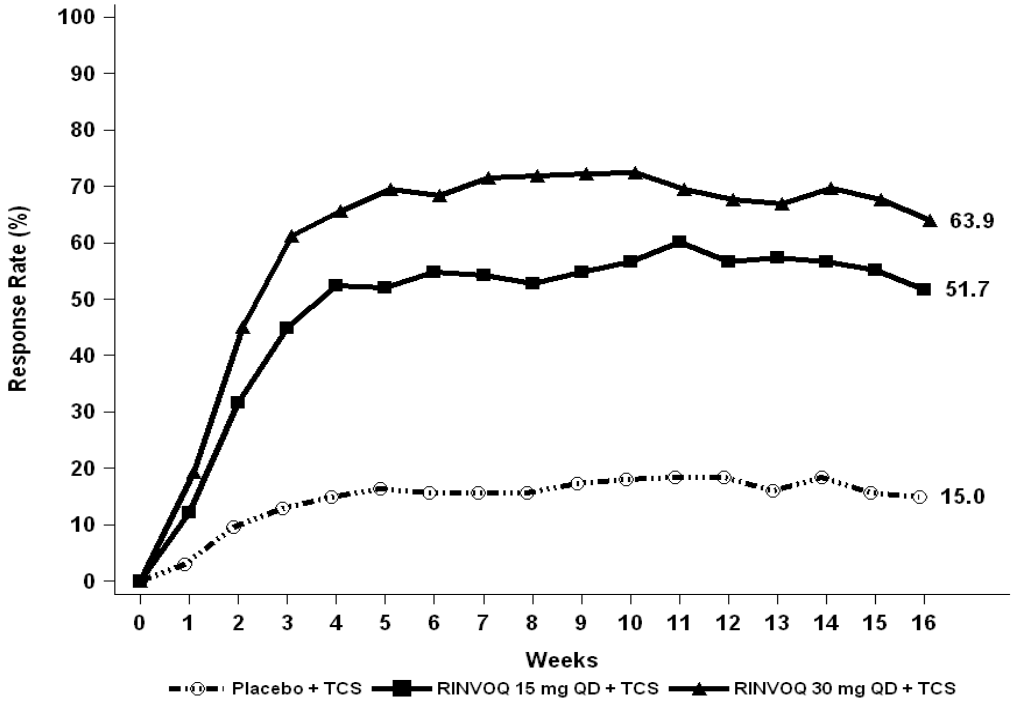


Figure 8. Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in AD UP Study



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

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 AD and the impact of AD on health-related quality of life compared to placebo at Week 16 (Table 16). A significantly greater proportion of patients treated with Rinvoq achieved clinically meaningful reductions in AD 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 AD 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 AD 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 16).

Table 16. 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

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 542 adolescents aged 12 to 17 years with moderate to severe atopic dermatitis were randomised across the three Phase 3 studies, of which 344 were evaluated for the primary analysis. Adolescents in the primary analysis were randomised to 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 17). The adverse event profile in adolescents was generally similar to that in adults. Safety and efficacy of Rinvoq in adolescents weighing less than 40 kg and in patients less than 12 years of age with atopic dermatitis have not been established.

Table 17. Efficacy Results of Rinvoq for Adolescents at Week 16

Study	**MEASURE UP 1**			**MEASURE UP 2**			**AD UP**		
Treatment Group	PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg	PBO + TCS	UPA 15 mg + TCS	UPA 30 mg + TCS
Number of adolescent subjects randomised	40	42	42	36	33	35	40	39	37
% responders									
vIGA-AD 0/1 [a,b]	7.5%	38.1%	69.0%	2.8%	42.4%	62.5%	7.5%	30.8%	64.9%
EASI 75[a]	8.3%	71.4%	83.3%	13.9%	66.7%	74.5%	30.0%	56.4%	75.7%
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	15.4% N=39	45.0% N=40	54.8% N=42	2.8% N=36	33.3% N=30	50.0% N=34	13.2% N=38	41.7% N=36	54.5% N=33

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

Results at Week 16 were maintained through Week 76 in adolescents treated with RINVOQ 15 mg or 30 mg.

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 18). 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. The studies include long-term extensions for up to 5 years (SELECT-PsA 1) and 3 years (SELECT-PsA 2).

Table 18. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-PsA 1	Non-biologic 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 = biologic 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
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-biologic 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 19, Figure 9). 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 20). 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-biologic 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-biologic DMARDs (≤ 1 or >1).

Figure 9. Percent of Patients Achieving ACR 20 in SELECT-PsA 1

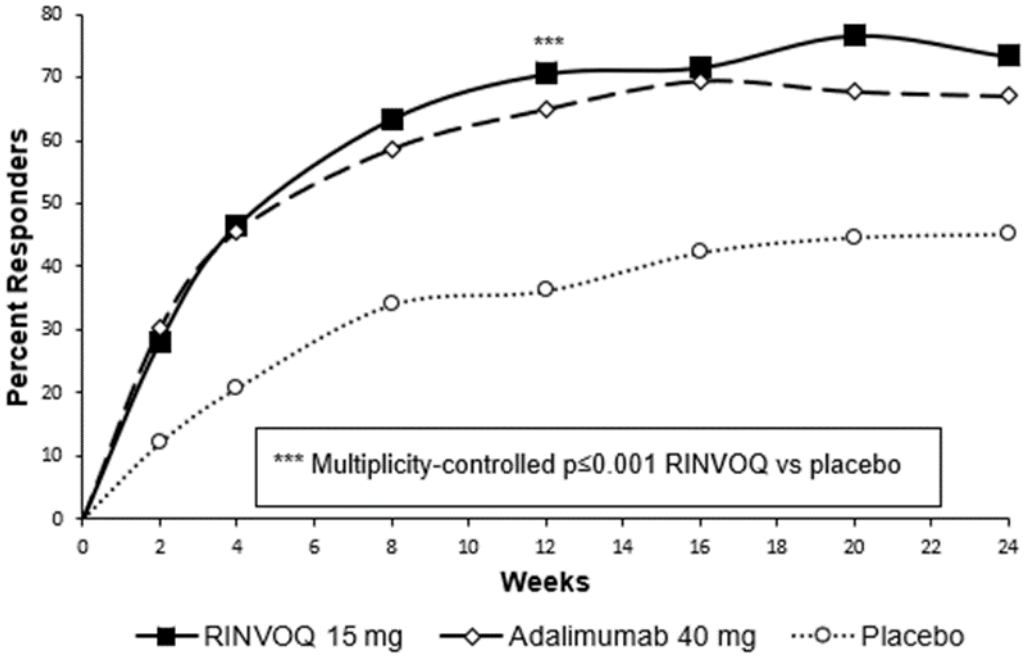


Table 19. Clinical Response

Study	SELECT-PsA 1 non-biologic 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,i]	67	20	59[f]
Week 56		74	69		60
ACR50 (% of patients)					
Week 12	13	38[f]	38	5	32[f]
Week 24	19	52[f,i]	44	9	38[f]
Week 56		60[i]	51		41
ACR70 (% of patients)					
Week 12	2	16[f]	14	1	9[f]
Week 24	5	29[f,i]	23	1	19[f]
Week 56		41[h]	31		24
MDA (% of patients)					
Week 12	6	25[f]	25	4	17[f]
Week 24	12	37[e]	33	3	25[e]
Week 56		45	40		29
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]
Week 56		59	54		43
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]
Week 56		75	74		51
PASI75 (% of patients)[c]					
Week 16	21	63[e]	53	16	52[e]
Week 24	27	64[f]	59	19	54[f]
Week 56		65	61		52
PASI90 (% of patients)[c]					
Week 16	12	38[f]	39	8	35[f]
Week 24	17	42[f]	45	7	36[f]
Week 56		49	47		41
PASI100 (% of patients)[c]					
Week 16	7	24[f]	20	6	25[f]
Week 24	10	27[f]	28	5	22[f]
Week 56		35	31		27
sIGA 0/1 (% of patients)[d]					
Week 16	11	42[e]	39	9	37[e]
Week 24	12	45[f]	41	10	33[f]
Week 56		52	47		33

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
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 24/56, 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≤0.01 upadacitinib vs adalimumab comparison
[i.] nominal p<0.05 upadacitinib vs adalimumab comparison

Table 20. Components of ACR Response (mean change from baseline)

Study	SELECT-PsA 1 non-biologic 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[d]	-10.3	-6.2	-12.4[d]
Week 24	-9.2	-13.7[d]	-12.5	-6.6	-14.0[d]
Week 56		-16.2	-15.8		-18.0
Number of swollen joints (0-66)					
Week 12	-5.3	-7.9[d]	-7.6	-4.8	-7.1[d]
Week 24	-6.3	-9.0[d]	-8.6	-5.6	-8.3[d]
Week 56		-10.1	-10.2		-9.4
Patient assessment of pain[a]					
Week 12	-0.9	-2.3[d]	-2.3	-0.5	-1.9[d]
Week 24	-1.4	-3.0[d, f]	-2.6	-0.7	-2.2[d]
Week 56		-3.5[g]	-3.0		-2.8
Patient global assessment[a]					
Week 12	-1.2	-2.7[d]	-2.6	-0.6	-2.3[d]
Week 24	-1.6	-3.4[d, e]	-2.9	-0.8	-2.6[d]
Week 56		-3.8[f]	-3.2		-3.1
Disability index (HAQ-DI)[b]					
Week 12	-0.14	-0.42[c, g]	-0.34	-0.10	-0.30[c]
Week 24	-0.19	-0.51[d, e]	-0.39	-0.08	-0.33[d]
Week 56		-0.56[f]	-0.44		-0.38
Physician global assessment[a]					
Week 12	-2.1	-3.6[d]	-3.4	-1.4	-3.1[d]
Week 24	-2.8	-4.3[d]	-4.1	-1.8	-3.8[d]
Week 56		-5.0	-4.8		-4.7
hsCRP (mg/L)					
Week 12	-1.3	-7.1[d]	-7.6	0.3	-6.6[d]
Week 24	-2.1	-7.6[d]	-7.3	-0.9	-6.3[d]
Week 56		-7.8	-7.2		-6.5

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.
[c.] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[d.] nominal p≤0.001 upadacitinib vs placebo comparison
[e.] nominal p≤0.001 upadacitinib vs adalimumab comparison
[f.] nominal p≤0.01 upadacitinib vs adalimumab comparison
[g.] nominal p<0.05 upadacitinib vs adalimumab comparison

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 21). 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 21. 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[c]	0.01
Week 56[a]	0.44	-0.05[d]	-0.06
Erosion Score, mean change from baseline			
Week 24	0.12	-0.03[d]	0.01
Week 56[a]	0.30	-0.03[d]	-0.05
Joint Space Narrowing Score, mean change from baseline			
Week 24	0.10	-0.00[f]	-0.02
Week 56[a]	0.14	-0.03[e]	-0.03
Proportion of patients with no radiographic progression[b]			
Week 24	92	96[f]	95
Week 56[a]	89	97[d]	94

Abbreviations:
ADA = adalimumab; PBO = placebo; UPA= upadacitinib
[a] All placebo data at Week 56 derived using linear extrapolation
[b] No progression defined as mTSS change ≤0.5
[c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[d] nominal p≤0.001 upadacitinib vs placebo comparison
[e] nominal p≤0.01 upadacitinib vs placebo comparison
[f] 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 19), 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.

<u>Non-radiographic Axial Spondyloarthritis</u>

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 22). The study included a long-term extension for up to 2 years.

Table 22. Clinical Trial Summary

Study Name	Population (n)[a]	Treatment Arms	Key Outcome Measures
SELECT-AXIS 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, a significantly greater proportion of patients treated with Rinvoq 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 23, Figure 10). Time to onset of efficacy was rapid across measures with greater 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 10. Percent of Patients Achieving ASAS40

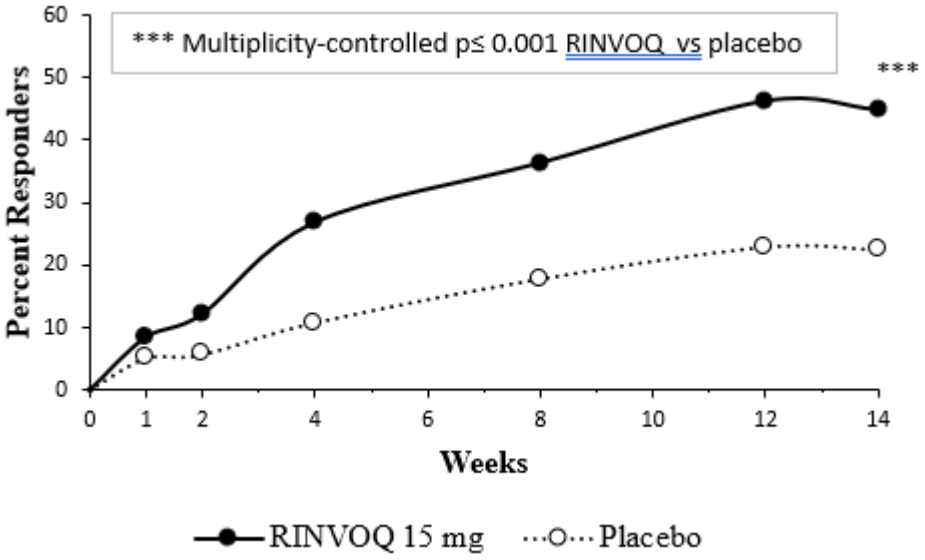


Table 23. Clinical Response

	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	-1.80[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]

ASDAS Major Improvement (%)		
Week 14	8.5	23.7[c]
Week 52	20.4	37.8[c]
hsCRP mg/L (Change from baseline)		
Week 14	-1.45	-6.50[c]
Week 52	-2.62	-6.91[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 23.

Table 24. 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 24).

Patients treated with Rinvoq 15 mg showed significant improvements in total back pain and nocturnal back pain compared to placebo at Week 14. These improvements were observed as early as Week 2 for total back pain and Week 4 for nocturnal back pain.

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.

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.

Improvements in BASFI, total and nocturnal back pain, 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.

<u>Ankylosing Spondylitis</u>

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 25). Both studies included a long-term extension for up to 2 years.

Table 25. 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	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)

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 = biologic 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 26, Figure 11 and Figure 12). 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 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 27).

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.

Figure 11. Percent of Patients Achieving ASAS40 in SELECT-AXIS 1

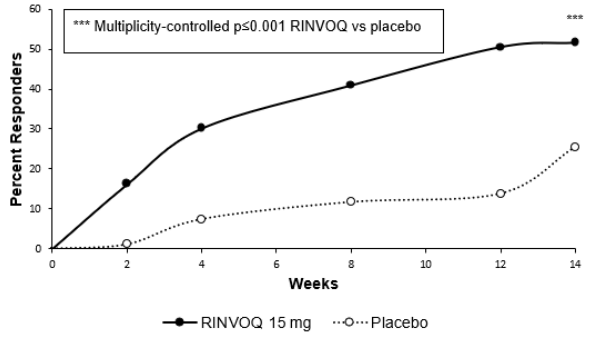


Figure 12. Percent of Patients Achieving ASAS40 in SELECT-AXIS 2

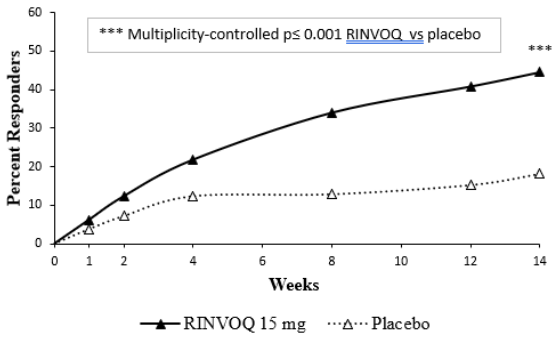


Table 26. Clinical Response

Study	SELECT AXIS 1 bDMARD-naïve		SELECT-AXIS 2 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]	10.1	44.1[a]

Week 52		85.9		65.8
Week 104		86.8		71.1
ASDAS Major Improvement (% of patients)				
Week 14	5.3	32.3[c]	4.8	30.3[c]
Week 52		55.8		52.7
Week 104		55.2		62.0
hsCRP mg/L (Change from baseline)				
Week 14	0.18	-8.20[c]	0.43	-10.90[c]
Week 52		-7.29		-9.45
Week 104		-8.03		-10.92

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; multiplicity-controlled endpoint in SELECT-AXIS 2.
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). 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, efficacy was maintained through 2 years as assessed by the endpoints presented in Table 26.

Table 27. Components of ASAS Response (mean change from baseline)

Study	**SELECT-AXIS 1 bDMARD- naïve**		**SELECT-AXIS 2 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]				
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 27).

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. Improvements in total and nocturnal back pain were observed as early as Week 2.

In SELECT-AXIS 2, patients treated with Rinvoq 15 mg showed significant improvements in total back pain and nocturnal back pain compared to placebo at Week 14. These improvements were observed as early as Week 1 for total back pain and Week 2 for nocturnal back pain.

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, improvements in BASFI and pain were maintained through 2 years for patients receiving Rinvoq 15 mg.

In SELECT-AXIS 2, patients treated with Rinvoq 15 mg showed significant improvements in health-related quality of life and overall health as measured by ASQoL and ASAS Health Index, respectively, compared to placebo at Week 14. Improvements in ASQoL and ASAS Health Index were also observed in SELECT-AXIS 1 compared to placebo at Week 14. Improvements in ASQoL and ASAS Health Index were maintained through 2 years.

In SELECT-AXIS 2, 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, 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. 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, patients treated with Rinvoq 15 mg showed significant improvement in spinal mobility compared to placebo as measured by change from baseline in Bath Ankylosing Spondylitis

Metrology Index (BASMI) at Week 14. Improvements in BASMI were also observed in 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, 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.

Giant Cell Arteritis

The efficacy and safety of Rinvoq 15 mg once daily were assessed in SELECT-GCA, a Phase 3 randomised, double-blind, multicenter, placebo-controlled study in patients 50 years of age and older with new-onset or relapsing giant cell arteritis. SELECT-GCA was a 52-week study in which 428 patients were randomised in a 2:1:1 ratio and dosed once daily with Rinvoq 15 mg, upadacitinib 7.5 mg, or placebo. All patients received background corticosteroid therapy. The Rinvoq and upadacitinib-treated groups followed a pre-specified corticosteroid taper regimen with the aim to reach 0 mg by 26 weeks, while the placebo-treated group followed a pre-specified corticosteroid taper regimen with the aim to reach 0 mg by 52 weeks. The primary endpoint was the proportion of patients achieving sustained remission at Week 52 as defined by the absence of giant cell arteritis signs and symptoms from Week 12 through Week 52 and adherence to the protocol-defined corticosteroid taper regimen. The study included a 52-week extension for a total study duration of up to 2 years.

Clinical Response

Rinvoq 15 mg and a 26-week corticosteroid taper showed superiority in achieving corticosteroid-free sustained remission at Week 52 compared to placebo and a 52-week corticosteroid taper (Table 28).

Treatment effects in subgroups (gender, age, race, prior use of interleukin-6 inhibitor, new-onset or relapsing giant cell arteritis, baseline corticosteroid dose, and giant cell arteritis with or without polymyalgia rheumatica) were consistent with the results in the overall study population.

Table 28. Clinical response in SELECT-GCA

Treatment Group	PBO + 52-week corticosteroid taper N= 112	UPA 15mg + 26-week corticosteroid taper N= 209	Treatment Difference (95% CI)
Sustained remission at Week 52[a]	29.0%	46.4%	17.1%[e] (6.3, 27.8)
Sustained complete remission at Week 52[b]	16.1%	37.1%	20.7%[f] (11.3, 30.2)
Complete remission at Week 52[c]	19.6%	50.2%	30.3%[f] (20.4, 40.2)
Complete remission at Week 24[c]	36.1%	57.2%	20.8%[f] (9.7, 31.9)
Cumulative corticosteroid exposure through Week 52 (median)[f]	2882.0 mg N=90[i]	1615.0 mg N=180[i]	
Time to first GCA flare through Week 52[d]			0.57 [e,g] (0.399, 0.826)
Patients with one or more GCA flares through Week 52[d]	55.6%	34.3%	0.47 [e,h] (0.29, 0.74)

Abbreviations:
ESR = erythrocyte sedimentation rate
GCA = giant cell arteritis
hsCRP = high sensitivity C-reactive protein
PBO = placebo; UPA = upadacitinib
[a] Sustained remission is defined as having achieved both the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol-defined corticosteroid taper regimen
[b] Sustained complete remission is defined as having achieved absence of GCA signs and symptoms from Week 12 through Week 52, normalisation of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52, normalisation of hsCRP to < 1 mg/dL without elevation to ≥ 1 mg/dL (on 2 consecutive visits) from Week 12 through Week 52, and adherence to the protocol-defined corticosteroid taper regimen
[c] Complete remission is defined as having achieved absence of GCA signs and symptoms, normalisation of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met), normalisation of hsCRP to < 1 mg/dL, and adherence to the protocol-defined corticosteroid taper regimen
[d] GCA flare is defined as an event representing recurrence of GCA signs or symptoms or an ESR measurement > 30 mm/hr (attributable to GCA) and requiring an increase in corticosteroid dose, and is only considered after all of the 3 following criteria are met: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no corticosteroid dose increase. Subjects who do not have an assessment that meets all 3 criteria are considered as having a GCA flare at baseline. Time to first GCA flare is calculated from the time when all three criteria above are met. Subjects who meet all 3 criteria above but never experience GCA flare are censored at the last assessment
[e] p≤0.01
[f] p≤0.001
[g] Hazard ratio
[h] Odds ratio
[i] Number of subjects who stayed in the study for 52 weeks

Treatment with Rinvoq 15 mg and a 26-week corticosteroid taper resulted in improvements in the components of corticosteroid-free sustained complete remission at Week 52 compared to placebo and a 52-week corticosteroid taper (Table 29).

Table 29. Components of sustained complete remission at Week 52

Treatment Group	PBO + 52-week corticosteroid taper N= 112	UPA 15mg + 26-week corticosteroid taper N= 209
Absence of GCA signs and symptoms[a]	29.8%	46.3%
Normalisation of ESR[b]	23.8%	47.0%
Normalisation of hsCRP[c]	25.0%	52.6%
Adherence to protocol-defined corticosteroid taper regimen	39.3%	58.4%

[a] Patients who did not have any signs or symptoms of GCA recorded from Week 12 through Week 52

[b] ESR to ≤ 30 mm/hr; (if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52

[c] hsCRP < 1 mg/dL, without elevation to ≥ 1 mg/dL (on 2 consecutive visits) from Week 12 through Week 52

Cumulative corticosteroid exposure

The cumulative corticosteroid exposure at Week 52 was significantly lower in patients treated with Rinvoq 15 mg and a 26-week corticosteroid taper compared to those treated with placebo and a 52-week corticosteroid taper (Table 28). The median cumulative corticosteroid exposure above the protocol-defined cumulative corticosteroid exposure through Week 52 was lower in patients treated with Rinvoq 15 mg compared to those treated with placebo (20.0 mg vs 512.5 mg, respectively).

Giant Cell Arteritis Flares

A significantly lower proportion of patients treated with Rinvoq 15 mg and a 26-week corticosteroid taper experienced at least one giant cell arteritis flare compared to those treated with placebo and a 52-week corticosteroid taper through Week 52. In addition, the risk of flare in patients treated with Rinvoq 15 mg and a 26-week corticosteroid taper was significantly lower compared to those treated with placebo and a 52-week corticosteroid taper as measured by time to first flare through Week 52 (Table 28).

Health-Related Outcomes

Fatigue was assessed using FACIT-Fatigue score. Patients treated with Rinvoq 15 mg and a 26-week corticosteroid taper experienced significantly greater improvement from baseline compared to placebo and a 52-week corticosteroid taper in FACIT-Fatigue score at Week 52.

Health-related quality of life was assessed using SF-36. Patients receiving Rinvoq 15 mg and a 26-week corticosteroid taper experienced significantly greater improvement from baseline compared to placebo and a 52-week corticosteroid taper in the Physical Component Summary score of SF-36 at Week 52.

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 a 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 30.

Table 30. 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 was moderate (aMS ≤7) in 61% and 60% of patients and severe (aMS >7) in 39% and 40% of patients, in UC-1 and UC-2 respectively.

Results of the primary endpoint of clinical remission at Week 8 and secondary endpoints are listed in Table 31.

Table 31. 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%
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%

	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)**
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])

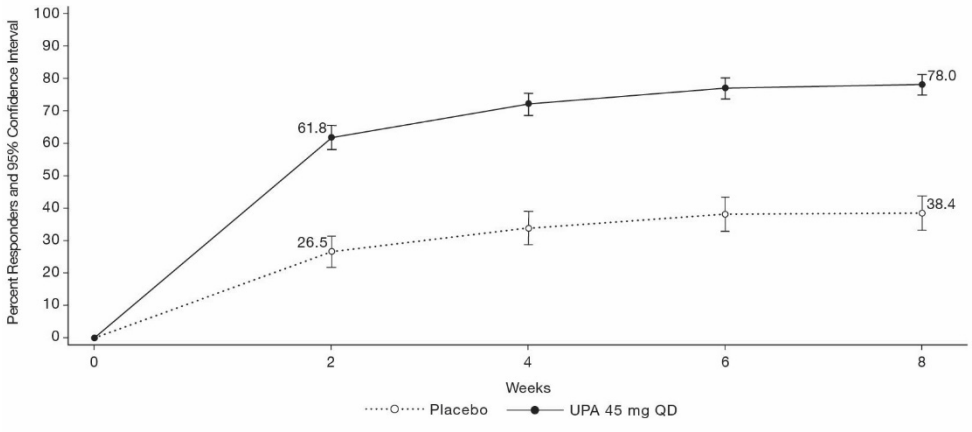
Disease Activity and Symptoms

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 31).

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 corticosteroids treatment, the rates were 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 13. 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 13. 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 31).

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 faecal 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 31.

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 32.

Table 32. 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%
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])

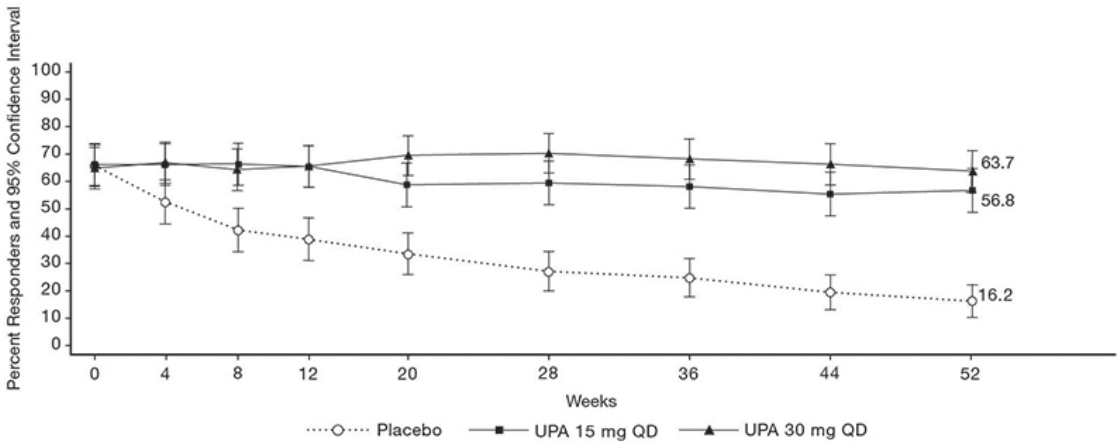
[i] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue [defined as mucosal healing in UC-3 protocol]).

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 32).

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 14).

Figure 14. 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 32).

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 faecal 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 32).

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 randomised 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.

Clinical 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 33). 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 33). A significantly greater proportion of patients achieved clinical remission at Week 4 compared to placebo (Table 33).

In CD-1 and CD-2, a greater proportion of patients treated with Rinvoq 45 mg (58% and 71%, respectively) compared to placebo (30% and 43%, respectively) achieved enhanced clinical response per SF/APS (≥ 60% decrease in average daily very soft or liquid SF and/or ≥ 35% decrease in average daily APS from baseline and neither greater than baseline, or clinical remission per SF/APS) at Week 12. Enhanced clinical response per SF/APS was achieved as early as Week 2.

In both studies, patients receiving Rinvoq 45 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score at Week 12 compared to placebo.

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 33). In CD-1 and CD-2, a greater proportion of patients treated with Rinvoq 45 mg (14% and 19%, respectively) compared to placebo (0% and 5%, respectively) achieved SES-CD 0-2.

Table 33. Proportion of Patients Meeting Primary and Additional Efficacy Endpoints in Induction Studies CD-1 and CD-2

Study	CD-1 (U-EXCEED)			CD-2 (U-EXCEL)		
Treatment Group	**PBO N=171**	**UPA 45 mg N=324**	**Treatment Difference (95% CI)**	**PBO N=176**	**UPA 45 mg N=350**	**Treatment Difference (95% CI)**
Co-Primary Endpoints at Week 12						
Clinical remission[a]	14%	40%	26% (19, 33)*	22%	51%	29% (21, 36)*
Prior biologic failure				N=78 14%	N=161 47%	33% (22, 44)
Without prior biologic failure				N=98 29%	N=189 54%	26% (14, 37)
Endoscopic response[b]	4%	35%	31% (25, 37)*	13%	46%	33% (26, 40)*
Prior biologic failure				N=78 9%	N=161 38%	29% (19, 39)
Without prior biologic failure				N=98 16%	N=189 52%	36% (25, 46)
Additional Endpoints at Week 12						
Clinical remission per CDAI[c]	21%	39%	18% (10, 26)*	29%	49%	21% (13, 29)*
Clinical response (CR-100)[d]	27%	51%	23% (14, 31)*	37%	57%	20% (11, 28)*
Corticosteroid-free clinical remission[a,e]	N=60 7%	N=108 37%	30% (19, 41)*	N=64 13%	N=126 44%	33% (22, 44)*
Endoscopic remission[f]	2%	19%	17% (12, 22)*	7%	29%	22% (16, 28)*
Mucosal healing[g]	N=171 0%	N= 322 17%	17% (13, 21)***	N=174 5%	N=349 25%	20% (14, 25)***
Early Onset Endpoints						
Clinical remission at Week 4[a]	9%	32%	23% (17, 30)*	15%	36%	21% (14, 28)*
CR-100 at Week 2[d]	12%	33%	21% (14, 28)*	20%	32%	12% (4, 19)**

Abbreviation: PBO = placebo, UPA = upadacitinib
* $p < 0.001$, 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 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
[g] SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at baseline

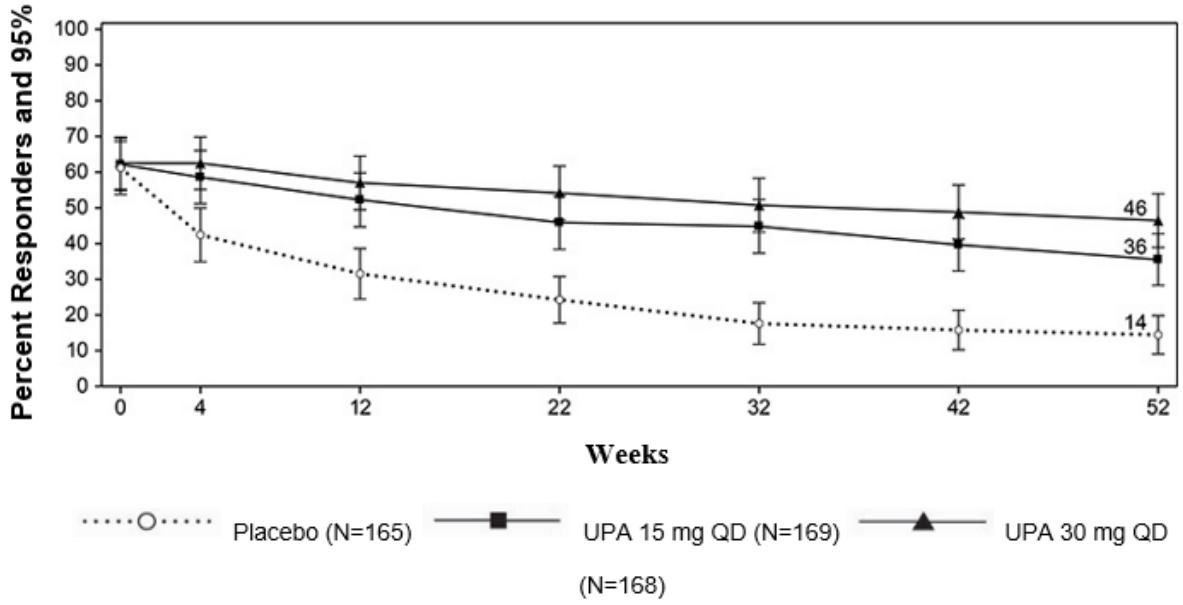
Maintenance Study (CD-3)

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.

Clinical 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 15, Table 34).

Figure 15. Proportion of Patients Achieving Clinical Remission in Maintenance Study CD-3



A greater proportion of patients treated with Rinvoq achieved enhanced clinical response per SF/APS at Week 52 compared to placebo (43%, 55%, and 20% for Rinvoq 15 mg, Rinvoq 30 mg, and placebo, respectively).

Patients receiving Rinvoq 30 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score at Week 52 compared to placebo.

Table 34. Proportion of Patients Meeting Primary and Additional Efficacy Endpoints at Week 52 in Maintenance Study CD-3

Treatment Group	PBO[+] N=165	UPA 15 mg N=169	UPA 30 mg N=168	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Co-Primary Endpoints					
Clinical remission[a]	14%	36%	46%	22% (14, 30)[*]	32% (23, 40)[*]
Prior biologic failure	N=126 9%	N=124 32%	N=127 43%	24% (14, 33)	34% (24, 44)
Without prior biologic failure	N=39 33%	N=45 44%	N=41 59%	12% (-9, 33)	26% (5, 47)
Endoscopic response[b]	7%	28%	40%	21% (14, 28)[*]	34% (26, 41)[*]
Prior biologic failure	N=126 4%	N=124 23%	N=127 39%	19% (11, 27)	35% (26, 44)
Without prior biologic failure	N=39 18%	N=45 40%	N=41 44%	22% (3, 41)	26% (7, 45)
Additional Endpoints					
Clinical remission per CDAI[c]	15%	37%	48%	24% (15, 32)[*]	33% (24, 42)[*]
Clinical response (CR-100)[d]	15%	41%	51%	27% (18, 36)[*]	36% (28, 45)[*]
Corticosteroid-free clinical remission[a,e]	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 remission[g]	5%	19%	29%	14% (8, 21)[*]	24% (16, 31)[*]
Mucosal healing[h]	N=164 4%	N=167 13%	N=168 24%	10% (4, 16)[***]	21% (14, 27)[***]
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 randomised to receive placebo at the start of maintenance therapy
[*] $p < 0.001$, adjusted treatment difference (95% CI)
[**] $p < 0.01$, adjusted treatment difference (95% CI)
[***] nominal $p < 0.001$ UPA vs PBO comparison, adjusted treatment difference (95% CI)
[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
[h] SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at baseline
[i] Clinical remission and endoscopic remission

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 34). A greater proportion of patients treated with Rinvoq 15 mg and 30 mg (11% and 21%, respectively) compared to placebo (3%) achieved SES-CD 0-2 at Week 52. Corticosteroid-free endoscopic remission among patients on steroid at baseline was achieved in a greater proportion of patients treated with Rinvoq 15 mg and 30 mg (17% and 25%, respectively) compared to placebo (3%) at Week 52.

Resolution of Extra-intestinal Manifestations

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

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 randomised 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 randomised 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.

Health-related Quality of Life Outcomes

Health-related quality of life was assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form (36) Health Survey (SF-36), the European Quality of Life 5 Dimensions Visual Analog Scale (EQ-5D VAS), the Work Productivity and Activity Impairment Questionnaire-Crohn's Disease (WPAI-CD), and the Crohn’s Symptom Severity (CSS).

In CD-1 and CD-2, patients treated with Rinvoq achieved greater improvement from baseline in IBDQ total score, all IBDQ domain scores including bowel symptoms, systemic symptoms, emotional function, and social function, SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores, and EQ-5D VAS at Week 12 compared to placebo. These improvements

were maintained in patients treated with Rinvoq 15 mg and 30 mg for IBDQ total score, EQ-5D VAS, and SF-36 MCS scores, and with Rinvoq 30 mg for SF-36 PCS score through Week 52 in CD-3.

Patients treated with Rinvoq achieved greater reductions from baseline in impairment while working, overall work impairment, and activity impairment at Week 12 compared to placebo in CD-1 and CD-2; and additionally greater reduction in work time missed in CD-1, as assessed by the WPAI-CD questionnaire. The improvements were maintained through Week 52 in patients treated with Rinvoq 15 mg and 30 mg for activity impairment in CD-3.

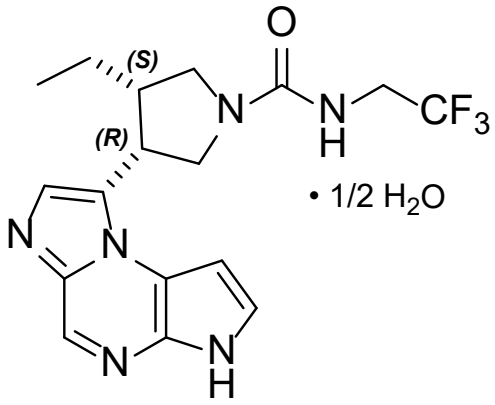
Patients treated with Rinvoq achieved greater improvements from baseline in Crohn's-related symptoms and sleep impact as assessed by CSS questionnaire at Week 12 compared to placebo in CD-1 and CD-2. These improvements were maintained in patients treated with Rinvoq 15 mg and 30 mg through Week 52 in CD-3.

Physicochemical properties

Upadacitinib is a white to light brown powder with the following 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).

The strength of upadacitinib is based on anhydrous upadacitinib. The solubility of upadacitinib in water is 38 to less than 0.2 mg/mL across a pH range of 2 to 9 at 37°C.

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. The chemical structure of upadacitinib is:



CAS number

1310726-60-3

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 35.

Table 35. 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	52
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 mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function. For dosing in patients with renal impairment **see DOSAGE AND METHOD OF ADMINISTRATION.**

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, non-radiographic axial spondyloarthritis, atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, giant cell arteritis, ulcerative colitis and Crohn's disease.

5.3 Pre-clinical safety data

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

Genotoxicity

Upadacitinib was not mutagenic or genotoxic based on the results of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberrations.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each 15 mg, 30 mg and 45 mg modified release tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, silica (colloidal anhydrous), and magnesium stearate. Film coating contains polyvinyl alcohol, macrogol, talc, titanium dioxide (E171) and iron oxide red (E172).

Rinvoq 15 mg additionally contains iron oxide black (E172) in the film coating.

Rinvoq 45 mg additionally contains iron oxide yellow (E172) in the film coating.

6.2 Incompatibilities

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

6.3 Shelf life

Rinvoq modified release tablets: 24 months.

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.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

The following presentations are available for each strength:

Starter Pack (7 tablets) – 1 carton containing one blister with 7 tablets.

Monthly Pack (28 tablets) – 1 carton containing four blisters with 7 tablets in each blister.

Not all presentations may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
NEW ZEALAND
PH: 0800 900 030

9 DATE OF FIRST APPROVAL

19 November 2020

10 DATE OF REVISION

09 March 2026

Summary table of changes

Section changed	Summary of new information
4.8 Adverse effects	Addition of semen discolouration