1. NAME OF THE MEDICINAL PRODUCT

RINVOQ EXTENDED-RELEASE TABLET 15 MG
RINVOQ EXTENDED-RELEASE TABLET 30 MG
RINVOQ EXTENDED-RELEASE TABLET 45 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ 15 mg extended-release tablets

Each extended-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib.

RINVOQ 30 mg extended-release tablets

Each extended-release tablet contains upadacitinib hemihydrate, equivalent to 30 mg of upadacitinib.

RINVOQ 45 mg extended-release tablets

Each extended-release tablet contains upadacitinib hemihydrate, equivalent to 45 mg of upadacitinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablet

RINVOQ 15 mg extended-release tablets

Purple 14 x 8 mm, oblong biconvex extended-release tablets imprinted on one side with ‘a15’.

RINVOQ 30 mg extended-release tablets

Red 14 x 8 mm, oblong biconvex extended-release tablets imprinted on one side with ‘a30’.

RINVOQ 45 mg extended-release tablets

Yellow to mottled yellow 14 x 8 mm, oblong biconvex extended-release tablets imprinted on one side with ‘a45’.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis

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

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 methotrexate.

Non-radiographic Axial Spondyloarthritis

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

Ankylosing Spondylitis

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

Atopic Dermatitis

RINVOQ is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy and whose disease is not adequately controlled with topical medications or for whom topical treatments are otherwise medically inadvisable.

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.

4.2 Posology and method of administration

Treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which upadacitinib is indicated.

Posology

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

The recommended dose of upadacitinib is 15 mg once daily.

Atopic Dermatitis

Adults

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

A dose of 30 mg once daily may be considered for patients with high disease burden or for patients with an inadequate response to 15 mg once daily, if clinically warranted and based on benefit-risk assessment.

The lowest effective dose for maintenance should be used.

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

Adolescents (from 12 to 17 years of age)

The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.

Concomitant Topical Therapies

Upadacitinib 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.

Consideration should be given to discontinuing upadacitinib treatment in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

Ulcerative Colitis

Induction

The recommended induction dose of upadacitinib is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by Week 8, upadacitinib 45 mg once daily may be continued for an additional 8 weeks (see sections 4.8 and 5.1). Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance

The recommended maintenance dose of upadacitinib is 15 mg or 30mg 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 (e.g. severe disease, pancolitis) 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 upadacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Interactions

For patients with ulcerative colitis receiving strong inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole, clarithromycin), the recommended induction dose is 30 mg once daily and the recommended maintenance dose is 15 mg once daily (see section 4.5).

Dose Initiation

Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) that is < 0.5 x 10^9 cells/L, an absolute neutrophil count (ANC) that is < 1 x 10^9 cells/L or who have haemoglobin (Hb) levels that are < 8 g/dL (see sections 4.4 and 4.8).

Dose Interruption

Treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

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

Table 1. Laboratory Measures and Monitoring Guidance

Laboratory measure	Action	Monitoring guidance
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1 x 10^9 cells/L and may be restarted once ANC returns above this value	Evaluate at baseline and then no later than 12 weeks after initiation of treatment. Thereafter evaluate according to individual patient management.
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is < 0.5 x 10^9 cells/L and may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb is < 8 g/dL and may be restarted once Hb returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	Evaluate at baseline and thereafter according to routine patient management.
Lipids	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special Populations

Elderly

For atopic dermatitis, doses higher than 15 mg once daily are not recommended in patients aged 65 years and older (see Section 4.8).

For ulcerative colitis, doses higher than 15 mg once daily for maintenance therapy are not recommended in patients aged 65 years and older (see section 4.8). The safety and efficacy of upadacitinib in patients aged 75 and older have not yet been established.

There are limited data in patients aged 75 years and older.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment (see section 5.2). Upadacitinib should be used with caution in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) 15 to < 30 ml/min/1.73m^2) as described in Table 2. The use of upadacitinib has not been studied in subjects with end stage renal disease.

Table 2. Recommended Dose for Severe Renal Impairment

Severe renal impairment	Indication	Recommended once daily dose

	Rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, atopic dermatitis	15 mg
	Ulcerative colitis	Induction: 30 mg
		Maintenance: 15 mg

Hepatic Impairment

No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see section 5.2). Upadacitinib should not be used in patients with severe (Child Pugh-C) hepatic impairment (see section 4.3).

Paediatric Population

Atopic Dermatitis

The safety and efficacy of RINVOQ in children with atopic dermatitis below the age of 12 years have not been established. No data are available. No clinical exposure data are available in adolescents < 40 kg (see section 5.2).

Rheumatoid Arthritis, Psoriatic Arthritis, Non-radiographic Axial Spondyloarthritis, Ankylosing Spondylitis, Ulcerative Colitis

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.

Method of Administration

RINVOQ is to be taken orally once daily with or without food and may be taken at any time of the day. Tablets should be swallowed whole and should not be split, crushed, or chewed in order to ensure the entire dose is delivered correctly.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active tuberculosis (TB) or active serious infections (see section 4.4).
- Severe hepatic impairment (see section 4.2).
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Immunosuppressive Medicinal Products

Combination with other potent immunosuppressants such as azathioprine, ciclosporin, 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.

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving upadacitinib. The most frequent serious infections reported with upadacitinib included pneumonia and cellulitis (see section 4.8). Cases of bacterial meningitis have been reported in patients receiving upadacitinib. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/oesophageal candidiasis, and cryptococcosis were reported with upadacitinib.

Upadacitinib should not be initiated in patients with an active, serious infection, including localised infections.

Consider the risks and benefits of treatment prior to initiating upadacitinib 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.

A higher rate of serious infections was observed with upadacitinib 30 mg compared to upadacitinib 15 mg.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib. Upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib therapy should be interrupted if the patient is not responding to antimicrobial therapy. Upadacitinib therapy may be resumed once the infection is controlled.

As there is a higher incidence of infections in the elderly ≥ 65 years of age, caution should be used when treating this population.

Tuberculosis

Patients should be screened for tuberculosis (TB) before starting upadacitinib therapy. Upadacitinib should not be given to patients with active TB (see section 4.3). Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with previously untreated latent TB or in patients with risk factors for TB infection.

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

Patients should be monitored 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), was reported in clinical studies (see section 4.8). The risk of herpes zoster appears to be higher in patients treated with upadacitinib in Japan. If a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with upadacitinib. 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 upadacitinib, a liver specialist should be consulted.

Vaccination

No data are available on the response to vaccination with live vaccines in patients receiving upadacitinib. Use of live, attenuated vaccines during or immediately prior to upadacitinib therapy is not recommended. Prior to and during upadacitinib 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 **PHARMACOLOGICAL PROPERTIES**).

Mortality

In a large randomized active-controlled post-marketing safety study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with a different JAK inhibitor compared to Tumor Necrosis Factor (TNF) blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib.

Malignancy

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

In a large randomized active-controlled post-marketing safety study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of malignancies (excluding non-melanoma skin cancer [NMSC]) was observed with a different JAK inhibitor compared to TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Malignancies were observed in clinical studies of upadacitinib. A higher rate of malignancies, driven by NMSC, was observed with upadacitinib 30 mg compared to upadacitinib 15 mg.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib, particularly in patients with a known malignancy (other than successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-Melanoma Skin Cancer

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

Major Adverse Cardiovascular Events (MACE)

In a large randomized active-controlled post-marketing safety study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke

was observed with a different JAK inhibitor compared with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Events of MACE were observed in clinical studies of upadacitinib.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Haematological Abnormalities

Absolute Neutrophil Count (ANC) < 1 x 10^9 cells/L, Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L and haemoglobin < 8 g/dL were reported in ≤1 % of patients in clinical trials (see section 4.8). Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 10^9 cells/L, ALC < 0.5 x 10^9 cells/L or haemoglobin < 8 g/dL observed during routine patient management (see section 4.2).

Lipids

Treatment with upadacitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see section 4.8). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy, although evidence is limited. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined (see section 4.2 for monitoring guidance).

Hepatic Transaminase Elevations

Treatment with upadacitinib was associated with an 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, upadacitinib therapy should be interrupted until this diagnosis is excluded.

Thrombosis

In a large, randomised, post-marketing safety study of a different JAK inhibitor in rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, deep vein thrombosis (DVT), and pulmonary embolism (PE) were observed compared to those treated with TNF blockers.

Events of DVT and PE were observed in clinical trials for upadacitinib.

Upadacitinib should be used with caution in patients at high risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, patients undergoing major surgery, and prolonged immobilisation. If symptoms of thrombosis occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving upadacitinib in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue upadacitinib and institute appropriate therapy (see section 4.8).

Gastrointestinal Perforations

Events of gastrointestinal perforations have been reported in clinical trials (see section 4.8) and from post-marketing sources.

Upadacitinib 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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect the pharmacokinetics of upadacitinib

Upadacitinib is metabolised mainly by CYP3A4. Therefore, upadacitinib plasma exposures can be affected by medicinal products that strongly inhibit or induce CYP3A4.

Coadministration with CYP3A4 Inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, and grapefruit). In a clinical study, coadministration of upadacitinib with ketoconazole resulted in 70% and 75% increases in upadacitinib C_{max} and AUC, respectively. Upadacitinib 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. Upadacitinib 30 mg once daily dose is not recommended for patients with atopic dermatitis receiving chronic treatment with strong CYP3A4 inhibitors. For patients with ulcerative colitis using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily (for up to 16 weeks) and the recommended maintenance dose is 15 mg once daily. Food or drink containing grapefruit should be avoided during treatment with upadacitinib. Alternatives to strong CYP3A4 inhibitor medications should be considered when used in the long-term.

Coadministration with CYP3A4 Inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin and phenytoin), which may lead to reduced therapeutic effect of upadacitinib. In a clinical study, coadministration of upadacitinib after multiple doses of rifampicin (strong CYP3A inducer) resulted in approximately 50% and 60% decreases in upadacitinib C_{max} and AUC, respectively. Patients should be monitored for changes in disease activity if upadacitinib is co-administered with strong CYP3A4 inducers.

Methotrexate and pH modifying medicinal products (e.g., antacids or proton pump inhibitors) have no effect on upadacitinib plasma exposures.

Potential for upadacitinib to affect the pharmacokinetics of other medicinal products

Administration of multiple 30 mg or 45 mg once daily doses of upadacitinib to healthy subjects had a limited effect on midazolam (sensitive substrate for CYP3A) plasma exposures (24-26% decrease in midazolam AUC and C_{max}), indicating that upadacitinib 30 mg or 45 mg once daily may have a weak induction effect on CYP3A. In a clinical study, rosuvastatin and atorvastatin AUC were decreased by 33% and 23%, respectively, and rosuvastatin C_{max} was decreased by 23% following the administration of multiple 30 mg once daily doses of upadacitinib to healthy subjects. Upadacitinib had no relevant effect on atorvastatin C_{max} or on plasma exposures of ortho-hydroxyatorvastatin (major active

metabolite for atorvastatin). Administration of multiple 45 mg once daily doses of upadacitinib to healthy subjects led to a limited increase in AUC and C_{max} of dextromethorphan (sensitive CYP2D6 substrate) by 30% and 35%, respectively, indicating that upadacitinib 45 mg once daily may have a weak inhibitory effect on CYP2D6. No dose adjustment is recommended for CYP3A substrates, CYP2D6 substrates, rosuvastatin or atorvastatin when coadministered with upadacitinib.

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

4.6 Fertility, pregnancy and lactation

Women of Childbearing Potential

Women of childbearing potential should be advised to use effective contraception during treatment and for 4 weeks following the final dose of upadacitinib. Female paediatric patients and/or their parents/caregivers should be informed about the need to contact the treating physician once the patient experiences menarche while taking upadacitinib.

Pregnancy

There are no or limited data on the use of upadacitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed *in utero*.

Upadacitinib is contraindicated during pregnancy (see section 4.3).

If a patient becomes pregnant while taking upadacitinib the parents should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether upadacitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk (see section 5.3).

A risk to newborns/infants cannot be excluded.

Upadacitinib should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue upadacitinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of upadacitinib on human fertility has not been evaluated. Animal studies do not indicate effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Rheumatoid Arthritis

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) were upper respiratory tract infections, nausea, blood creatine phosphokinase (CPK) increased and cough. The most common serious adverse reactions were serious infections (see section 4.4).

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical studies.
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 3. Adverse Reactions

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

Description of selected adverse reactions

Infections

In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the upadacitinib 15 mg group was 27.4% compared to 20.9% in the placebo group. In methotrexate (MTX)-controlled studies, the frequency of infection over 12/14 weeks in the upadacitinib 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group. The overall

long-term rate of infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies (2,630 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 upadacitinib 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 upadacitinib 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 upadacitinib 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most common serious infection was pneumonia. The rate of serious infections remained stable with long-term exposure.

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

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

Opportunistic infections (excluding tuberculosis)

In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the upadacitinib 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 upadacitinib 15 mg monotherapy group and 0.2% in the MTX group. The overall long-term rate of opportunistic infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies was 0.6 events 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 upadacitinib 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 upadacitinib 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

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

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

Creatine phosphokinase

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, increases in CPK values were observed. CPK elevations > 5 x upper limit of normal (ULN) were reported in 1.0% and 0.3% of patients over 12/14 weeks in the upadacitinib 15 mg and placebo groups, respectively. Most elevations > 5 x ULN were transient and did not require treatment discontinuation. Mean CPK values increased by 4 weeks with a mean increase of 60 U/L at 12 weeks and then remained stable at an increased value thereafter including with extended therapy.

Neutropenia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, decreases in neutrophil counts below 1 x 10^9 cells/L in at least one measurement occurred in 1.1% and <0.1% of patients in the upadacitinib 15 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ANC < 1 x 10^9 cells/L (see section 4.2). Mean neutrophil counts decreased over 4 to 8 weeks. The decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

Psoriatic Arthritis

Overall, the safety profile observed in patients with active psoriatic arthritis treated with upadacitinib 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher incidence of acne and bronchitis was observed in patients treated with upadacitinib 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively). A higher rate of serious infections (2.6 events per 100 patient years and 1.3 events per 100 patient years, respectively) and hepatic transaminase elevations (ALT elevations Grade 3 and higher rates 1.4% and 0.4%, respectively) was observed in patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy. There was a higher rate of serious infections in patients ≥ 65 years of age, although data are limited.

Non-radiographic Axial Spondyloarthritis

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

Ankylosing Spondylitis

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

Atopic Dermatitis

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) were upper respiratory tract infections, acne, herpes simplex, blood creatine phosphokinase (CPK) increased and headache. The most common serious adverse reactions were serious infections (see section 4.4).

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from registrational clinical studies. 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 4. Adverse Reactions

System Organ Class	Very common	Common	Uncommon
Infections and Infestations	Upper respiratory tract infections (URTI)[a]	Herpes simplex[b] Herpes zoster Folliculitis Influenza Urinary tract infection	Pneumonia Oral candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancer[d]
Blood and lymphatic system disorders		Neutropaenia 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 CPK 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 group term

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

Description of selected adverse reactions

Infections

In the placebo-controlled period of the clinical studies, the frequency of infection over 16 weeks in the upadacitinib 15 mg and 30 mg groups was 39% and 43% compared to 30% in the placebo group, respectively. The long-term rate of infections for the upadacitinib 15 mg and 30 mg groups was 98.5 and 109.6 events per 100 patient-years, respectively.

In placebo-controlled clinical studies, the frequency of serious infection over 16 weeks in the upadacitinib 15 mg and 30 mg groups was 0.8% and 0.4% compared to 0.6% in the placebo group, respectively. The long-term rate of serious infections for the upadacitinib 15 mg and 30 mg groups was 2.3 and 2.8 events per 100 patient-years, respectively. The most common serious infection was pneumonia.

The frequencies of infection ADRs for upadacitinib compared to placebo were: URTI (22.6% for 15 mg and 25.4% for 30 mg vs 16.5% for placebo), pneumonia (0.3% for 15 mg and 0.2% for 30 mg vs 0.1% for placebo), herpes zoster (1.6% for 15 mg and 1.5% for 30 mg vs 0.6% for placebo), herpes simplex (4.1% for 15 mg and 8.4% for 30 mg vs 1.7% for placebo), folliculitis (2.1% for 15 mg and 3.2% for 30 mg vs 1.1% for placebo), influenza (2.1% for 15 mg and 1.5% for 30 mg vs 0.3% for placebo), and oral candidiasis (0.1% for 15 mg and 0.6% for 30 mg vs. 0% for placebo).

Opportunistic infections (excluding tuberculosis)

In the placebo-controlled period of the clinical studies, all opportunistic infections (excluding TB and herpes zoster) reported were eczema *herpeticum.* The frequency of eczema *herpeticum* over 16 weeks in the upadacitinib 15 mg and 30 mg groups was 0.7% and 0.8% compared to 0.4% in the placebo group, respectively. The long-term rate of eczema *herpeticum* for the upadacitinib 15 mg and 30 mg groups was 1.6 and 1.8 events per 100 patient-years, respectively. One case of esophageal candidiasis was reported with upadacitinib 30 mg.

The long-term rate of herpes zoster for the upadacitinib 15 mg and 30 mg groups was 3.5 and 5.2 events per 100 patient-years, respectively. Most of the herpes zoster events involved a single dermatome and were non-serious.

Hepatic transaminase elevations

In placebo-controlled studies, for up to 16 weeks, alanine transaminase (ALT) elevation ≥ 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 upadacitinib 15 mg, 30 mg and placebo, respectively. In these studies, 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 upadacitinib 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

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

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

Small increases in LDL cholesterol were observed after Week 16.

Creatine phosphokinase

In placebo-controlled studies for up to 12/14 weeks, dose-related increases in CPK values were observed. CPK elevations > 5 x upper limit of normal (ULN) were reported in 3.3%, 4.4% and 1.7% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. Most elevations > 5 x ULN were transient and did not require treatment discontinuation.

Neutropaenia

In placebo-controlled studies for up to 16 weeks, dose-related decreases in neutrophil counts below 1,000 cells/mm^3 in at least one measurement occurred in 0.4%, 1.3% and 0% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ANC < 1,000 cells/mm^3 (see section 4.2). Mean neutrophil counts decreased over 4 to 8 weeks. The decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

Elderly

Based on limited data in atopic dermatitis patients aged 65 years and older, there was a higher rate of overall adverse reactions with the upadacitinib 30 mg dose compared to the 15 mg dose.

Paediatric population

A total of 343 adolescents aged 12 to 17 years with atopic dermatitis were treated in the Phase 3 studies, of which 167 were exposed to 15 mg. The safety profile for upadacitinib 15 mg in adolescents was similar to that in adults. The safety and efficacy of the 30 mg dose in adolescents are still being investigated.

Ulcerative Colitis

Upadacitinib 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) randomized, double-blind, placebo-controlled clinical studies and a long-term extension study (see section 5.1) with a total of 1304 patients representing 1821 patient-years of exposure, of whom a total of 721 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 upadacitinib 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 upadacitinib 15 mg, of whom 131 were exposed for at least one year and 291 patients received at least one dose of upadacitinib 30 mg, of whom 137 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 5. 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 Urinary tract infection	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			

Specific Adverse Reactions

Infections

In the placebo-controlled induction studies, the frequency of infection over 8 weeks in the upadacitinib 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 upadacitinib 15 mg and 30 mg groups was 38.4% and 40.6%, respectively, and 37.6% in the placebo group. The long-term rate of infection for upadacitinib 15 mg and 30 mg was 73.8 and 82.6 events per 100 patient-years, respectively.

Serious Infections

In the placebo-controlled induction studies, the frequency of serious infection over 8 weeks in the upadacitinib 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 upadacitinib 45 mg. In the placebo-controlled maintenance study, the frequency of serious infection over 52 weeks in the upadacitinib 15 mg and 30 mg groups was 3.2%, and 2.4%, respectively, and 3.3% in the placebo group. The long-term rate of serious infection for the upadacitinib 15 mg and 30 mg groups was 4.1 and 3.9 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 upadacitinib 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 upadacitinib 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 upadacitinib 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) in the upadacitinib 15 mg and 30 mg groups was 0.8% and 0.4%, respectively, and 0.8% in the placebo group. The long-term rate of opportunistic infection (excluding tuberculosis and herpes zoster) for the upadacitinib 15 mg and 30 mg groups was 0.6 and 0.3 per 100 patient-years, respectively.

In the placebo-controlled induction studies over 8 weeks, the frequency of herpes zoster in the upadacitinib 45 mg group was 0.6% and 0% in the placebo group. The frequency of herpes zoster was 3.9% over 16-week treatment with upadacitinib 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of herpes zoster in the upadacitinib 15 mg and 30 mg groups was 4.4% and 4.0%, respectively, compared to 0% in the placebo group. The long-term rate of herpes zoster for the upadacitinib 15 mg and 30 mg groups was 5.7 and 6.3 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 upadacitinib 15 mg and 30 mg groups was 0.4%, 0.8%, respectively, and 0.4% in the placebo group. The long-term incidence rate of malignancies excluding NMSC for the upadacitinib 15 mg and 30 mg was 0.3 and 1.0 per 100 patient years, respectively.

Gastrointestinal Perforations

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

Thrombosis

In the placebo-controlled induction studies, the frequency of venous thrombosis (pulmonary embolism or deep vein thrombosis) over 8 weeks in the upadacitinib 45 mg group was 0.1% and 0.3% in the placebo group, respectively. No additional events of venous thrombosis were reported with upadacitinib 45 mg extended induction treatment. In the placebo-controlled maintenance study, the frequency of venous thrombosis over 52 weeks in the upadacitinib 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 upadacitinib 15 mg and 30 mg was 1.0 and 0.7 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 upadacitinib 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 4.0% of patients treated with upadacitinib 15 mg and 30 mg and 0.8% 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 upadacitinib 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

Elevations in lipid parameters were observed at 8 weeks of treatment with upadacitinib 45 mg and remained generally stable with longer-term treatment with upadacitinib 15 mg and 30 mg. Among

patients in the placebo-controlled induction studies with baseline values below the specified limits, the following frequencies of patients were observed to shift to above the specified limits on at least one occasion during 8 weeks (including patients who had an isolated elevated value):

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

Creatine phosphokinase elevations

In the placebo-controlled induction studies over 8 weeks, increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 2.2% and 0.3% of patients in the upadacitinib 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study over 52 weeks, CPK elevations > 5 x ULN were reported in 4.0% and 6.4% of patients in the upadacitinib 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 upadacitinib 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 upadacitinib 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 upadacitinib 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 0.8% of patients in the upadacitinib 15 mg and 30 mg groups and to 0.8% in the placebo group, respectively.

Anemia

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

Post Marketing Experience

The following adverse reactions have been identified during post-approval use of upadacitinib. 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.

- *Immune system disorders:* Hypersensitivity

4.9 Overdose

Upadacitinib was administered in clinical studies up to doses equivalent in daily AUC to 60 mg extended-release once daily. Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants ATC code: L04AA44

Mechanism of Action

Upadacitinib is a selective and reversible Janus Kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis 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.

In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Atopic dermatitis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus. Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15 and IFNγ) transduce signals via the JAK1 pathway and are involved in ulcerative colitis pathogenesis. JAK1 inhibition with upadacitinib modulates the signaling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of ulcerative colitis.

Pharmacodynamic effects

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.

hsCRP

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

Vaccine Studies

The influence of upadacitinib 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 upadacitinib 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 upadacitinib 15 mg.

The influence of upadacitinib on the humoral response following the administration of pneumococcal 13-valent conjugate vaccine was evaluated in 111 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg (n=87) or 30 mg (n=24). 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 upadacitinib 15 mg and 30 mg, respectively.

Clinical efficacy and safety

Rheumatoid Arthritis

The efficacy and safety of upadacitinib 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 6). 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.

The primary analysis for each of these studies included all randomised subjects who received at least 1 dose of study drug, and non-responder imputation was used for categorical endpoints.

Across the Phase 3 studies, the efficacy seen with upadacitinib 15 mg QD was generally similar to that observed with upadacitinib 30 mg QD.

Table 6: Clinical Trials 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: clinical remission (DAS28-CRP) at week 24 • Low disease activity (DAS28-CRP) • ACR50 • Radiographic progression (mTSS) • Physical function (HAQ-DI) • SF-36 PCS
SELECT-MONOTHERAPY	MTX-IR[b] (648)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	• Primary endpoint: low disease activity (DAS28-CRP) at week 14 • Clinical remission (DAS28-CRP) • ACR20 • Physical function (HAQ-DI) • SF-36 PCS • Morning stiffness
SELECT-NEXT	csDMARD-IR[c] (661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• Primary endpoint: low disease activity (DAS28-CRP) at week 12 • Clinical remission (DAS28-CRP) • ACR20 • Physical function (HAQ-DI) • SF-36 PCS • Low disease activity (CDAI)

			• Morning stiffness • FACIT-F
SELECT-COMPARE	MTX-IR[d] (1,629)	• Upadacitinib 15 mg • Placebo • Adalimumab 40 mg On background MTX	• Primary endpoint: clinical remission (DAS28-CRP) at week 12 • Low disease activity (DAS28-CRP) • ACR20 • Low disease activity (DAS28-CRP) vs adalimumab • Radiographic progression (mTSS) • Physical function (HAQ-DI) • SF-36 PCS • Low disease activity (CDAI) • Morning stiffness • FACIT-F
SELECT-BEYOND	bDMARD-IR[e] (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• Primary endpoint: low disease activity (DAS28-CRP) at week 12 • ACR20 • Physical function (HAQ-DI) • SF-36 PCS

Abbreviations: ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement; bDMARD = biologic disease-modifying anti-rheumatic drug, CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints, mTSS = modified Total Sharp Score, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, HAQ-DI = Health Assessment Questionnaire-Disability Index, SF-36 PCS = Short Form (36) Health Survey (SF-36) Physical Component Summary, CDAI = Clinical Disease Activity Index, FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue score, IR = inadequate responder, MTX = methotrexate, n = number randomised

[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 the studies, a significantly higher proportion of patients treated with upadacitinib 15 mg achieved low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX or adalimumab (Table 7). Compared to adalimumab, significantly higher rates of low disease activity were achieved at week 12 in SELECT-COMPARE. 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.

ACR Response

In all studies, more patients treated with upadacitinib 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo, MTX, or adalimumab (Table 7). Time to onset of efficacy

was rapid across measures with greater responses seen as early as Week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained through 3 years based on available long-term extension study results.

Treatment with upadacitinib 15 mg, alone or in combination with csDMARDs, resulted in improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment and hsCRP.

Table 7: 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 15 mg	MTX	UPA 15 mg	PBO	UPA 15 mg	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	314	317	216	217	221	221	651	651	327	169	164
Week											
LDA DAS28-CRP ≤3.2 (% of patients)											
12[a]/14[b]	28	53[g]	19	45[e]	17	48[e]	14	45[e,h]	29	14	43[e]
24[c]/26[d]	32	60[f]					18	55[g,h]	39		
48	39	59[g]						50[h]	35		
CR DAS28-CRP <2.6 (% of patients)											
12[a]/14[b]	14	36[g]	8	28[e]	10	31[e]	6	29[e,h]	18	9	29[g]
24[c]/26[d]	18	48[e]					9	41[g,h]	27		
48	29	49[g]						38[i]	28		
ACR20 (% of patients)											
12[a]/14[b]	54	76[g]	41	68[e]	36	64[e]	36	71[e,j]	63	28	65[e]
24[c]/26[d]	59	79[g]					36	67[g,i]	57		
48	57	74[g]						65[i]	54		
ACR50 (% of patients)											
12[a]/14[b]	28	52[g]	15	42[g]	15	38[g]	15	45[g,h]	29	12	34[g]
24[c]/26[d]	33	60[e]					21	54[g,h]	42		
48	43	63[g]						49[i]	40		
ACR70 (% of patients)											
12[a]/14[b]	14	32[g]	3	23[g]	6	21[g]	5	25[g,h]	13	7	12
24[c]/26[d]	18	44[g]					10	35[g,h]	23		
48	29	51[g]						36[h]	23		
CDAI ≤10 (% of patients)											
12[a]/14[b]	30	46[g]	25	35[l]	19	40[e]	16	40[e,h]	30	14	32[g]
24[c]/26[d]	38	56[g]					22	53[g,h]	38		
48	43	60[g]						47[h]	34		

Abbreviations: ADA = adalimumab; CDAI = Clinical Disease Activity Index; LDA = Low Disease Activity; PBO = placebo; UPA= upadacitinib

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

[b] SELECT-MONOTHERAPY

[c] SELECT-EARLY

[d] SELECT-COMPARE

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

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

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

[h] nominal p≤0.001upadacitinib vs adalimumab comparison

[i] nominal p≤0.01 upadacitinib vs adalimumab comparison
[j] nominal p<0.05 upadacitinib vs adalimumab comparison
[k] nominal p≤0.01 upadacitinib vs placebo or MTX comparison
[l] nominal p<0.05 upadacitinib vs MTX comparison
Note: Week 48-data derived from analysis on Full Analysis set (FAS) by randomised group using Non-Responder Imputation

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 24/26 and Week 48 in SELECT-EARLY and SELECT-COMPARE.

Treatment with upadacitinib 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo in combination with MTX in SELECT-COMPARE and as monotherapy compared to MTX in SELECT-EARLY (Table 8). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with upadacitinib 15 mg in both studies. Inhibition of progression of structural joint damage was maintained through Week 96 in both studies for patients receiving RINVOQ 15 mg.

Table 8: 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 Sharp Score, mean change from baseline					
Week 24[b]/26[c]	0.7	0.1[f]	0.9	0.2[g]	0.1
Week 48	1.0	0.03[e]	1.7	0.3[e]	0.4
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	74.3	89.9[e]	74.1	86.4[e]	87.9

[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] nominal p≤0.001 upadacitinib vs placebo or MTX comparison
[f] multiplicity controlled p≤0.01 upadacitinib vs placebo or MTX comparison
[g] multiplicity controlled p≤0.001 upadacitinib vs placebo or MTX comparison

Physical Function Response and Health-Related Outcomes

Treatment with upadacitinib 15 mg, alone or in combination with csDMARDs, resulted in a significantly greater improvement in physical function compared to all comparators as measured by HAQ-DI (see Table 9).

Table 9: Mean Change from Baseline in HAQ-DI[a,b]

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

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

[a] Data shown are mean

[b] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

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

[d] SELECT-MONOTHERAPY

[e] SELECT-EARLY

[f] SELECT-COMPARE

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

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

[i] nominal p≤0.01 upadacitinib vs adalimumab comparison

Improvement in HAQ-DI was maintained through 3 years for patients receiving upadacitinib 15 mg based on available results from SELECT-COMPARE and SELECT-EARLY.

In the studies SELECT-MONOTHERAPY, SELECT-NEXT, and SELECT-COMPARE, treatment with upadacitinib 15 mg resulted in a significantly greater improvement in the mean duration of morning joint stiffness compared to placebo or MTX.

In the clinical studies, upadacitinib treated patients reported significant improvements in patient-reported quality of life, as measured by the Short Form (36) Health Survey (SF-36) Physical Component Summary compared to placebo and MTX. Moreover, upadacitinib treated patients reported significant improvements in fatigue, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) compared to placebo.

Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in two Phase 3 randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis (Table 10). 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 10. 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: MDA = minimal disease activity; mTSS = modified Total Sharp Score; PASI = Psoriasis Area and Severity Index; SAPS = Self-Assessment of Psoriasis Symptoms; 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 11, Figure 1). 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 12).

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, and number of prior non-biologic DMARDs (≤ 1 or >1).

Figure 1. Percent of Patients Achieving ACR20 in SELECT-PsA 1

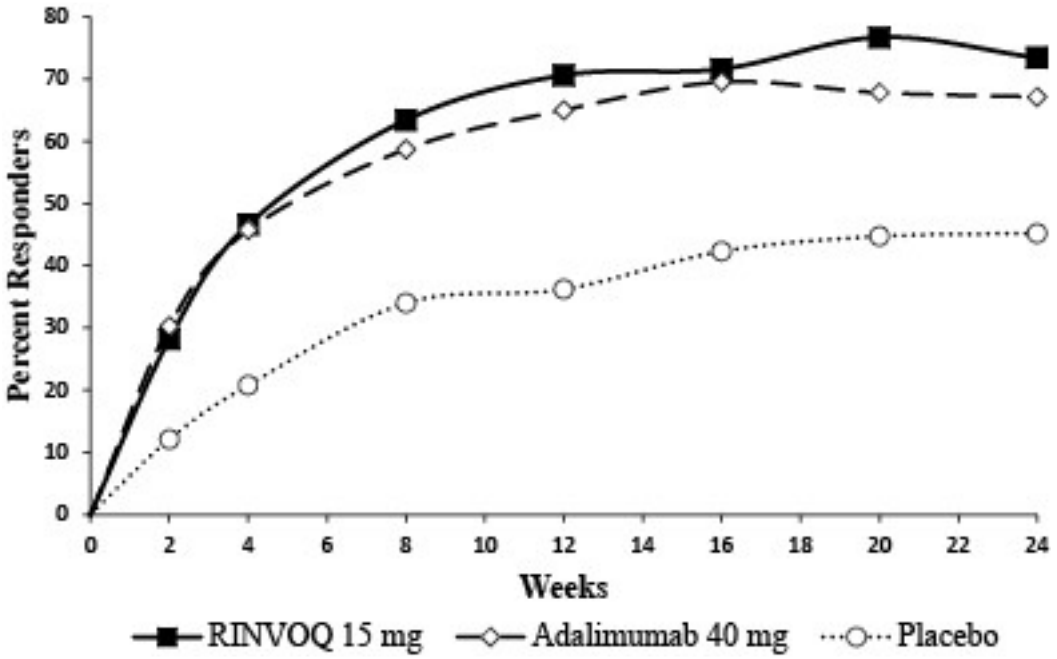


Table 11. Clinical Response

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

Patients who discontinued randomized treatment or were missing data at week of evaluation were imputed as non-responders in the analyses. For MDA, resolution of enthesitis, and resolution of dactylitis at Week 24/56, 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 12. 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

[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 13). Erosion and joint space narrowing scores were consistent with the overall 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 13. 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
[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 12), 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. 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.

SAPS change from baseline at Week 16 in SELECT-PsA 1 and SELECT-PsA 2 were –25.3 (95% CI: –27.3, –23.4) and –24.4 (95% CI: –27.5, –21.2), respectively, in patients receiving RINVOQ 15 mg, and –8.2 (95% CI: –10.2, –6.3) and –1.5 (95% CI: –4.7, 1.8), respectively, in patients receiving placebo.

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. Improvements from baseline were maintained through Week 56 in both studies.

Non-radiographic Axial Spondyloarthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in a randomized, 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 14). The study included a long-term extension for up to 2 years.

Table 14. Clinical Trial Summary

Study Name	**Population (n)[a]**	**Treatment Arms**	**Key Outcome Measures**
		• Upadacitinib 15 mg	Primary Endpoint: • ASAS40 at Week 14

SELECT-AXIS 2 (STUDY 2)	NSAID-IR[b,c] (314)	• Placebo	Key Secondary Endpoints at Week 14:
			• ASDAS-CRP
			  • SPARCC MRI score (SI joints)
			  • BASDAI 50
			• ASDAS Inactive Disease
			• Total Back Pain
			• Nocturnal Back Pain
			• ASDAS Low Disease Activity
			  • ASAS Partial Remission
			• BASFI (function)
			• AS Quality of Life
			• ASAS Health Index
			• ASAS20
			• BASMI (spinal mobility)
			  • MASES (enthesitis)

Abbreviations: ASAS40 = Assessment of SpondyloArthritis international Society ≥40% improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; NSAID = Nonsteroidal Anti-inflammatory Drug; SPARCC MRI = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging [a] Patients must have had objective signs of inflammation indicated by elevated C-reactive protein (CRP) (defined as > upper limit of normal), and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. [b] Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindication for NSAIDs [c] At baseline, 29.1% of the patients were on a concomitant csDMARD and 32.9% of the patients had an inadequate response or intolerance to bDMARD therapy.			

Clinical Response

In SELECT-AXIS 2 (STUDY 2), a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 15, Figure 2). 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 2. Percent of Patients Achieving ASAS40

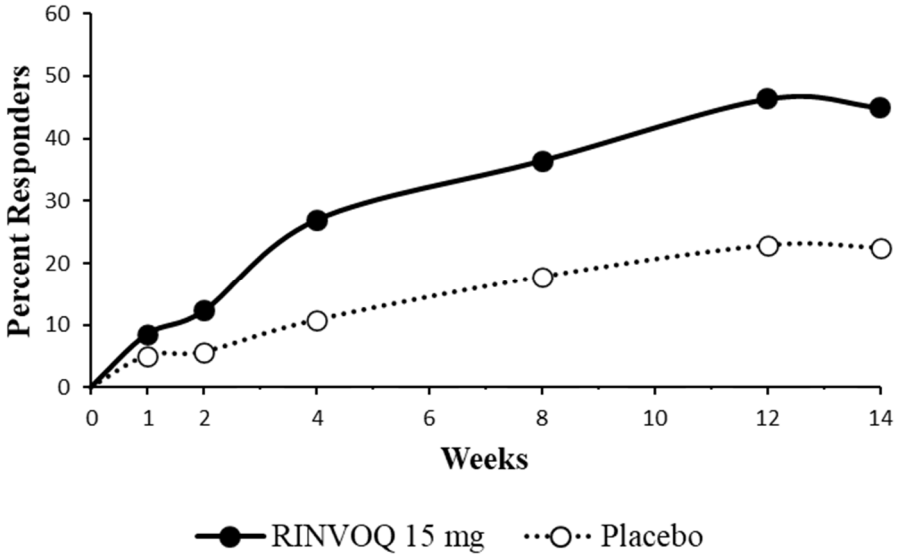


Table 15. Clinical Response at Week 14

	PBO (N=157)	**UPA 15 mg (N=156)**
ASAS40 (%)	22.5	44.9[a]
ASAS20 (%)	43.8	66.7[a]
ASAS Partial Remission (%)	7.6	18.6[b]
BASDAI 50 (%)	22.1	42.3[a]
ASDAS-CRP (Change from Baseline)	-0.71	-1.36[a]
ASDAS Inactive Disease (%)	5.2	14.1[b]
ASDAS Low Disease Activity (%)	18.3	42.3[a]
ASDAS Major Improvement (%)	8.5	23.7[c]
hsCRP mg/L (Change from Baseline)	-1.45	-6.50[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
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.

Table 16. Components of ASAS Response at Week 14 (mean change from baseline)

Treatment Group	**PBO (N=157)**	**UPA 15 mg (N=156)**
Patient Global Assessment of Disease Activity[a]	-1.87	-2.89[d]
Total Back Pain[a]	-2.00	-2.91[c]
BASFI[a]	-1.47	-2.61[c]
Inflammation[b]	-1.93	-3.05[d]

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

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 16).

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.

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.

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.

Ankylosing Spondylitis

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

Table 17. Clinical Trial Summary

Study Name	**Population (n)**	**Treatment Arms**	**Key Outcome Measures**
SELECT-AXIS 1	NSAID-IR[a,b] bDMARD-naïve (187)	• Upadacitinib 15 mg • Placebo	Primary Endpoint: • ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASAS Partial Remission • BASDAI 50 • ASDAS-CRP • BASFI • SPARCC MRI score (spine)
SELECT-AXIS 2 (STUDY 1)	bDMARD-IR[a,c,d] (420)	• Upadacitinib 15 mg • Placebo	Primary Endpoint: ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASDAS-CRP • SPARCC MRI score (spine) • BASDAI 50 • ASAS20

			• ASDAS Inactive Disease • Total Back Pain • Nocturnal Back Pain • ASDAS Low Disease Activity • BASFI (function) • ASAS Partial Remission • AS Quality of Life • ASAS Health Index • BASMI (spinal mobility) • MASES (enthesitis)
[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 18, Figures 3 and 4). Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 2 in SELECT-AXIS 1 and Week 4 in SELECT-AXIS 2 (STUDY 1) for ASAS40.

Treatment with RINVOQ 15 mg resulted in improvements in individual ASAS components, (patient global assessment of disease activity, total back pain assessment, inflammation, and function) and other measures of disease activity, including BASDAI at Week 14 compared to placebo (Table 19).

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 3. Percent of Patients Achieving ASAS40 in SELECT-AXIS 1

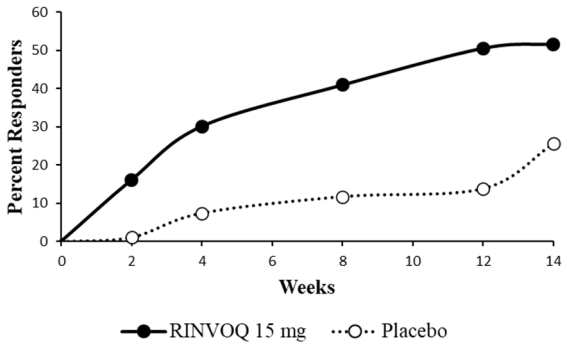


Figure 4. Percent of Patients Achieving ASAS40 in SELECT-AXIS 2 (STUDY 1)

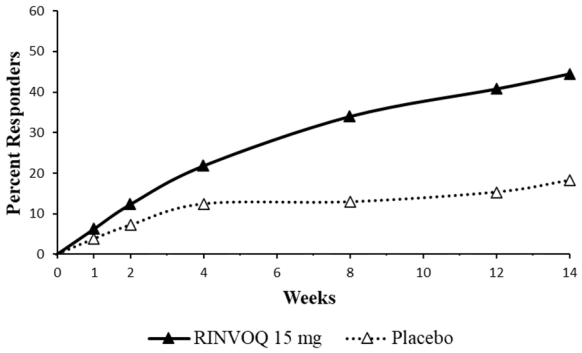


Table 18. Clinical Response

Study	**SELECT-AXIS 1 bDMARD-naïve**		**SELECT-AXIS 2 (STUDY 1) bDMARD-IR**	
Treatment Group	**PBO**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
N	94	93	209	211
ASAS40 (% of patients)				
Week 14	25.5	51.6[a]	18.2	44.5[a]
Week 52		80.2		
ASAS20 (% of patients)				

Week 14	40.4	64.5[c]	38.3	65.4[a]
Week 52		87.7		
ASAS Partial Remission (% of patients)				
Week 14	1.1	19.4[a]	4.3	17.5[a]
Week 52		50.0		
BASDAI 50 (% of patients)				
Week 14	23.4	45.2[b]	16.7	43.1[a]
Week 52		77.8		
ASDAS-CRP (Change from Baseline)				
Week 14	-0.54	-1.45[a]	-0.49	-1.52[a]
Week 52		-2.05		
ASDAS Inactive Disease (% of patients)				
Week 14	0	16.1[c]	1.9	12.8[a]
Week 52		46.2		
ASDAS Low Disease Activity (% of patients)[d]				
Week 14	10.6	49.5[c]	10.1	44.1[a]
Week 52		85.9		
ASDAS Major Improvement (% of patients)				
Week 14	5.3	32.3[c]	4.8	30.3[c]
Week 52		55.8		
hsCRP mg/L (Change from Baseline)				
Week 14	0.18	-8.20[c]	0.43	-10.90[c]
Week 52		-7.29		

[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 (STUDY 1).
For binary endpoints, Week 14 results are based on non-responder imputation (SELECT-AXIS 1) and on non-responder imputation in conjunction with multiple imputation (SELECT-AXIS 2 (STUDY 1)). For continuous endpoints, Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis. For binary and continuous endpoints, Week 52 results are based on as-observed data.

In SELECT-AXIS 1, efficacy was maintained through 2 years as assessed by the endpoints presented in Table 18.

Table 19. Components of ASAS Response (mean change from baseline)

Study	**SELECT-AXIS 1 bDMARD-naïve**		**SELECT-AXIS 2 (STUDY 1) bDMARD-IR**	
Treatment Group	**PBO**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
N	94	93	209	211
Patient Global Assessment of Disease Activity[a]				
Week 14	-1.31	-2.96[d]	-1.38	-2.97[d]
Week 52		-4.54		
Total Back Pain[a]				
Week 14	-1.68	-3.21[d]	-1.47	-3.00[c]
Week 52		-4.75		
BASFI[a]				
Week 14	-1.30	-2.29[c]	-1.09	-2.26[c]
Week 52		-3.71		
Inflammation[b]				

Week 14	-1.90	-3.15[d]	-1.59	-2.94[d]
Week 52		-4.80		

Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis; Week 52 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 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 the BASFI at Week 14 (Table 19).

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

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

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

In SELECT-AXIS 2 (STUDY 1), 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.

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

Enthesitis

In SELECT-AXIS 2 (STUDY 1), patients with pre-existing enthesitis treated with RINVOQ 15 mg showed significant improvement in enthesitis compared to placebo as measured by change from baseline in MASES at week 14. Improvements in MASES were also observed in SELECT-AXIS 1 compared to placebo at Week 14.

Spinal mobility

In SELECT-AXIS 2 (STUDY 1), patients treated with RINVOQ 15 mg showed significant improvement in spinal mobility compared to placebo as measured by change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14. Improvements in BASMI were also observed in SELECT-AXIS 1 compared to placebo at Week 14.

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. In SELECT-AXIS 1, improvement in inflammation as assessed by MRI was maintained through 2 years.

Atopic Dermatitis

The efficacy and safety of RINVOQ 15 mg and 30 mg once daily was assessed in three Phase 3 randomized, double-blind, multicenter studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 2584 patients 12 years of age and older (Table 20). RINVOQ was evaluated in 344 adolescent 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 randomized to RINVOQ were to continue receiving the same dose until week 136. Patients in the placebo group were re-randomized in a 1:1 ratio to receive RINVOQ 15 mg or 30 mg until week 136.

Table 20. 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
AD UP	• Upadacitinib 15 mg + TCS	Co-Primary Endpoints at Week 16: • EASI 75 • vIGA-AD 0/1

	• Upadacitinib 30 mg + TCS • Placebo + TCS	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 21). 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 21. 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 randomized	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]	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

(≥ 4-point improvement)						
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 randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4
[d] N = number of patients whose baseline Worst Pruritus NRS is > 1
[e] Percent 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**

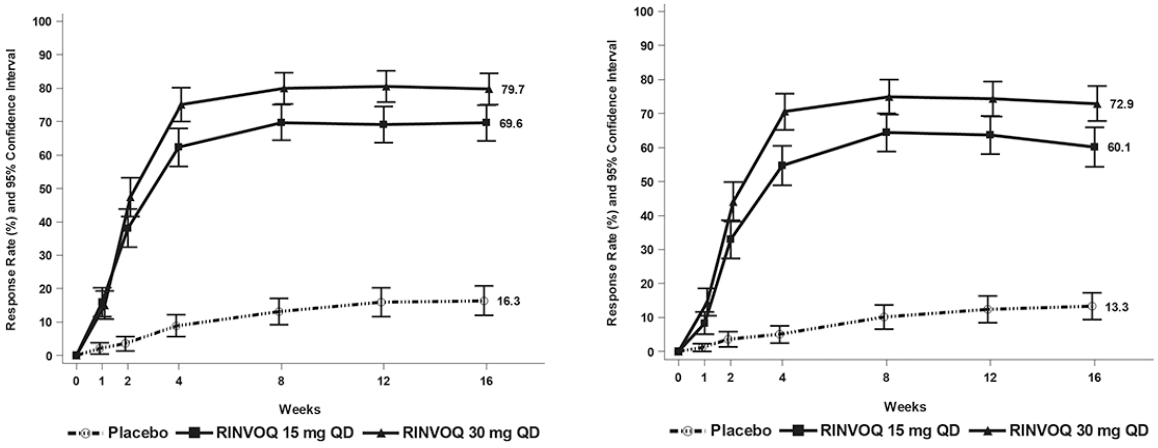
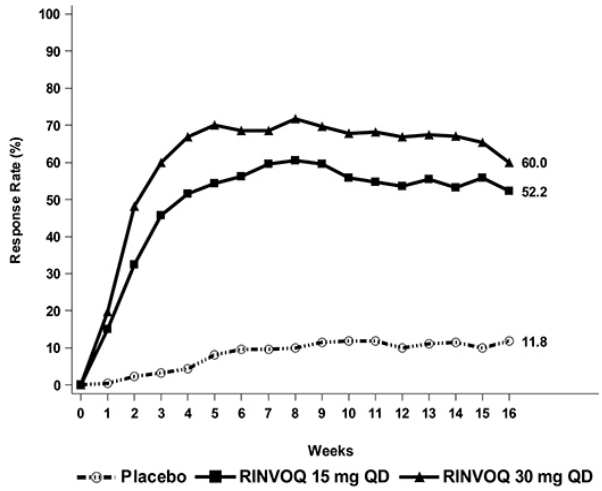
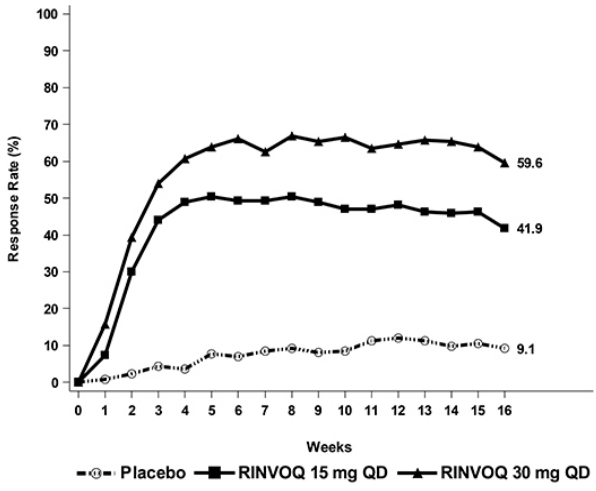


Figure 6. Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in monotherapy studies

MEASURE UP 1 **MEASURE UP 2**





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

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

Concomitant TCS Study (AD UP)

In AD UP, a significantly greater proportion of patients treated with RINVOQ 15 mg + TCS or 30 mg + TCS achieved vIGA AD 0 or 1 response and achieved EASI 75 compared to placebo + TCS at week 16 (Table 22). 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 22. Efficacy Results of RINVOQ + Concomitant TCS at Week 16

Treatment Group	**Placebo + TCS**	**UPA 15 mg + TCS**	**UPA 30 mg + TCS**
Number of subjects randomized	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)

[a] Based on number of subjects randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4
[d] N = number of patients whose baseline Worst Pruritus NRS is > 1
[e] Percent 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

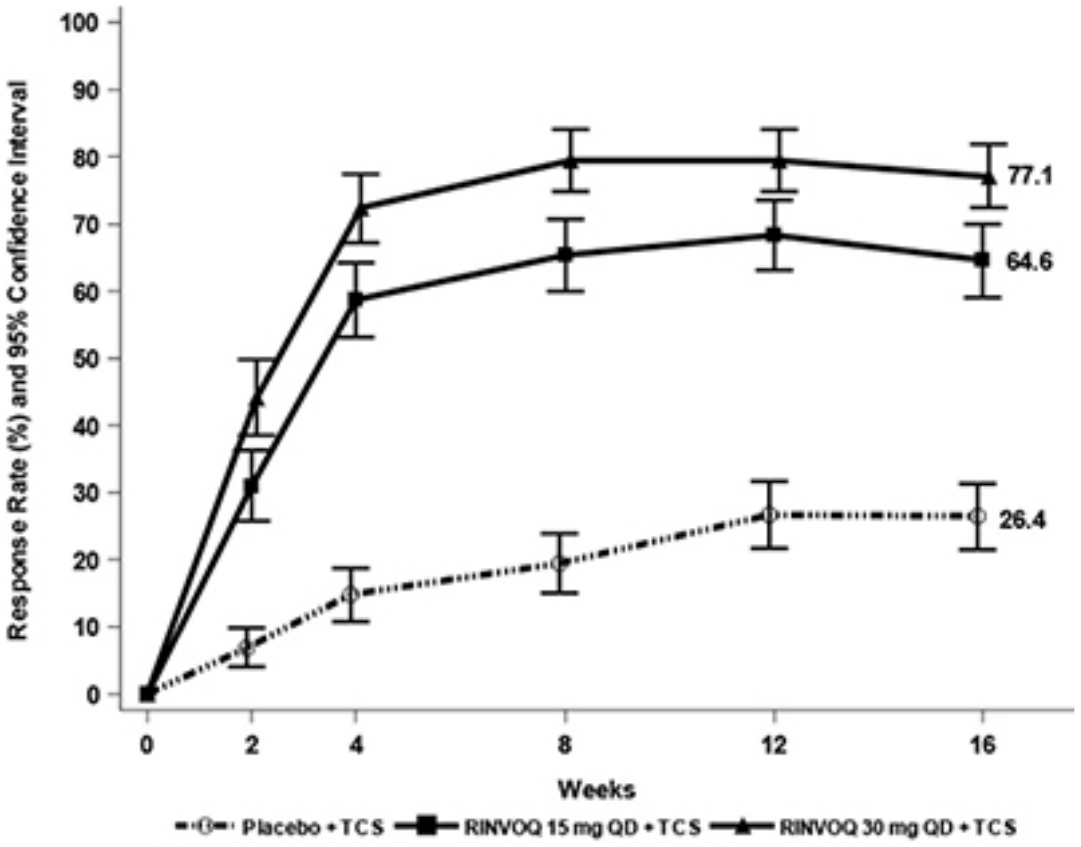
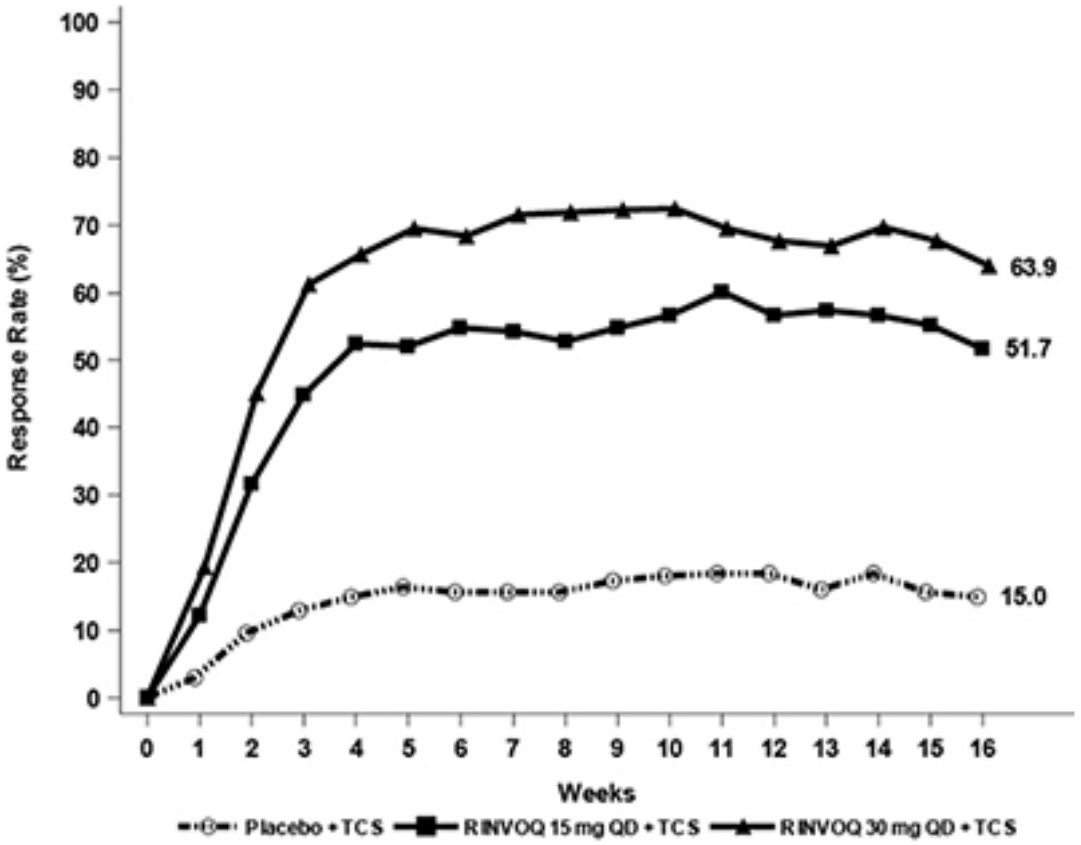


Figure 8. Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in AD UP Study



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 23). 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 23).

Table 23. 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 randomized	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

The threshold values specified correspond to the minimal clinically important difference (MCID) and was used to determine response.

[a] N = number of patients whose baseline score is greater than or equal to the MCID.

[b] ADerm-SS TSS-7 assesses itch while asleep, itch while awake, skin pain, skin cracking, pain caused by skin cracking, dry skin, and flaking due to AD.

[c] ADerm-IS Sleep assesses difficulty falling asleep, sleep impact, and waking up at night due to AD.

[d] ADerm-IS Daily Activities assesses AD's effect on household activities, physical activities, social activities, and concentration.

[e] ADerm-IS Emotional State assesses self-consciousness, embarrassment, and sadness due to AD.

[f] N = number of patients whose baseline DLQI score is > 1.

[g] N = number of patients whose baseline HADS-A or HADS-D is ≥ 8.

[h] multiplicity-controlled $p < 0.001$ upadacitinib vs placebo comparison.

Adolescent population

A total of 344 adolescents aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across the three Phase 3 studies to receive either 15 mg (N=114) or 30 mg (N=114) RINVOQ or matching placebo (N=116), in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the adolescents and adults (Table 24). The adverse event profile in adolescents was generally similar to that in adults.

Table 24. Efficacy Results of RINVOQ for Adolescents at Week 16

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

[a] Based on number of subjects randomized
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale
[c] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4

Ulcerative Colitis

The efficacy and safety of RINVOQ was evaluated in three multicenter, double-blind, placebo-controlled Phase 3 clinical studies: two replicate induction studies, UC-1 and UC-2, and a maintenance study UC-3.

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).

Table 25. Clinical Trial Summary

Study Name	**Population (n)**	**Treatment Arms**	**Key Outcome Measures**
Induction			
U-ACHIEVE (UC-1)	Biologic failure* (246/473)	• Upadacitinib 45 mg • Placebo	Primary Endpoint: • Clinical remission per Adapted Mayo score at Week 8

U-ACCOMPLISH (UC-2)	Without biologic failure[+] (227/473) Biologic failure(262/515) Without biologic failure (253/515)		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 (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 randomized 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, 39% and 37% of patients received corticosteroids, 1.1% and 0.6% of patients received methotrexate and 68% and 69% of patients received aminosalicylates. Concomitant use of thiopurine was not allowed during the studies. Patient disease activity was moderate (aMS ≥5, ≤7) in 61% and 60% of patients and severe (aMS >7) in 39% and 40% of patients.

Results of the primary endpoint of clinical remission at Week 8 and secondary endpoints are listed in Table 26.

Table 26. 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%
Endoscopic improvement[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 improvement[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%
Mucosal healing[g]	1.3%	10.7%	9.7%* (5.7, 13.7)	1.7%	13.5%	11.3%* (7.2, 15.3)
Prior biologic failure[+]	0	6.5%	6.5%	1.1%	9.2%	8.1%
Without prior biologic failure[+]	2.6%	15.4%	12.8%	2.4%	17.9%	15.5%
Quality of Life						
Change from Baseline in FACIT-F score	N = 125 2.8	N = 291 9.5	6.7* (4.79, 8.59)	N = 155 3.5	N = 312 9.4	6.0* (4.19, 7.73)
Change from Baseline in IBDQ total score	N = 125 21.7	N = 292 55.3	33.7* (27.02, 40.36)	N = 156 21.1	N = 315 52.2	31.2* (24.98, 37.36)

Abbreviation: PBO = placebo

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

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

[a] Per aMS: SFS ≤ 1 and not greater than Baseline, RBS = 0, ES of ≤ 1 without friability

[b] Per aMS: decrease ≥ 2 points and ≥ 30% from Baseline and a decrease in RBS ≥ 1 from Baseline or an absolute RBS ≤ 1

[c] ES of 0

[d] ES ≤1 without friability.

[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).

[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)

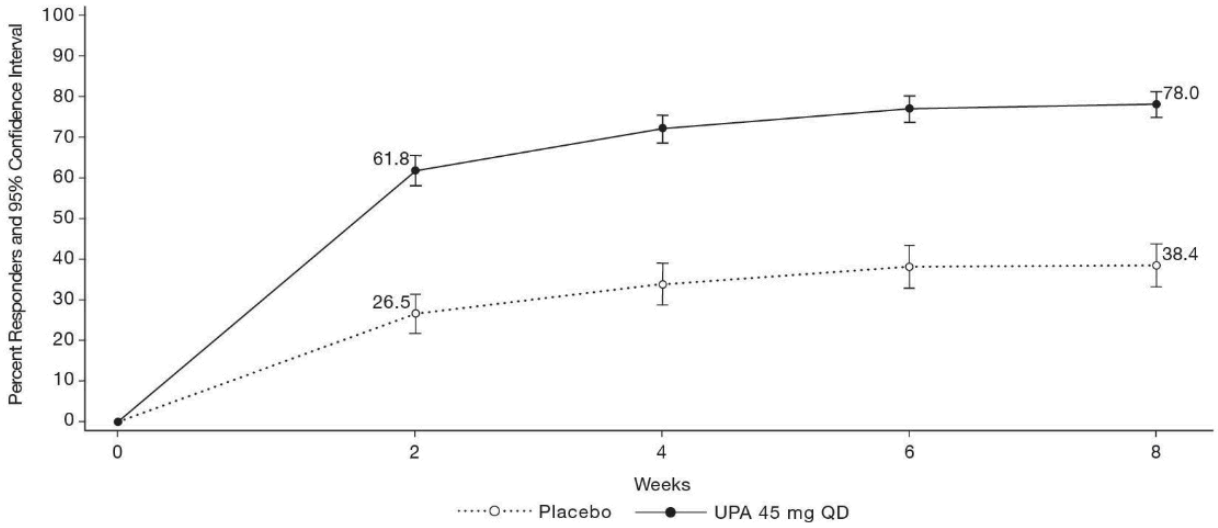
Disease Activity and Symptoms

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 26).

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



Endoscopic and Histologic Assessment

Normalization 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 26).

Biomarkers of Inflammation

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

Quality of Life

Patients treated with RINVOQ 45 mg once daily compared to placebo demonstrated significantly greater and clinically meaningful improvements in health-related quality of life measured by the inflammatory bowel disease questionnaire (IBDQ), see Table 26.

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 randomized 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 27.

Table 27. 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					
Endoscopic remission[e]	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%
Endoscopic improvement[f]	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%

Maintenance of endoscopic improvement[g]	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%
Histologic-endoscopic mucosal improvement[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%
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)

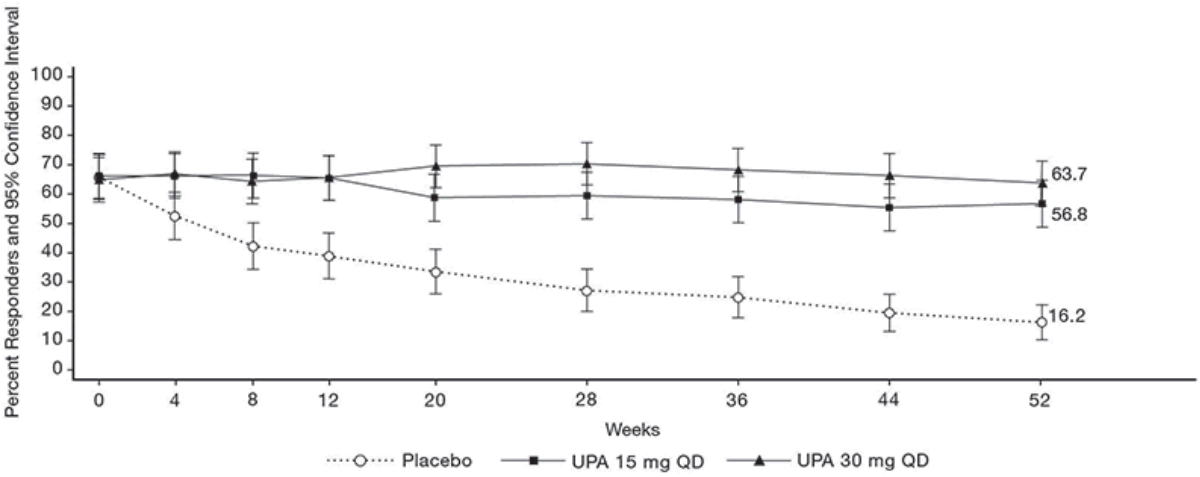
[+]The number of "Prior biologic failure" patients are 81, 71, and 73 in the placebo, RINVOQ 15 mg, and 30 mg group, respectively. The number of "Without prior biologic failure" patients are 68, 77, and 81 in the placebo, RINVOQ 15 mg, and 30 mg group, respectively.
[*] p <0.001, adjusted treatment difference (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 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] ES subscore = 0.
[f] ES ≤1 without friability.
[g] Maintain endoscopic improvement, ES ≤1 without friability, among patients with endoscopic improvement in induction.
[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).
[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).

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 27).

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 10).

Figure 10. 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 endoscopic improvement at Week 52 (ES ≤1 without friability) was seen in a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg once daily compared to placebo among patients who achieved endoscopic improvement at the end of induction (see Table 27).

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

Biomarkers of Inflammation

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

Quality of Life

Patients treated with RINVOQ compared to placebo demonstrated significantly greater and clinically meaningful improvement in health-related quality of life as measured by inflammatory bowel disease questionnaire (IBDQ). See Table 27.

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.

Absorption

Following oral administration of upadacitinib extended-release formulation, upadacitinib is absorbed with a median T_{max} of 2 to 4 hours. Coadministration of upadacitinib with a high-fat meal had no clinically relevant effect on upadacitinib exposures (increased AUC by 29% and C_{max} by 39% to 60%). In clinical trials, upadacitinib was administered without regard to meals (see section 4.2). *In vitro*, upadacitinib is a substrate for the efflux transporters P-gp and BCRP.

Distribution

Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components, as indicated by the blood to plasma ratio of 1.0.

Metabolism

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

Elimination

Following single dose administration of [^{14}C]-upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent substance in urine (24%) and faeces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours.

Special populations

Renal impairment

Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild (estimated glomerular filtration rate 60 to 89 mL/min/1.73 m^2), moderate (estimated glomerular filtration rate 30 to 59 mL/min/1.73 m^2), and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m^2) 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 section 4.2.

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 (Child-Pugh C) hepatic impairment.

Paediatric population

The pharmacokinetics of upadacitinib have not yet been evaluated in paediatric patients with rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis and ulcerative colitis (see section 4.2).

Upadacitinib pharmacokinetics and steady-state concentrations are similar for adults and adolescents 12 to 17 years of age with atopic dermatitis. The posology in adolescent patients 30 kg to < 40 kg was determined using population pharmacokinetic modelling and simulation.

The pharmacokinetics of upadacitinib in paediatric patients (< 12 years of age) with atopic dermatitis have not been established.

Intrinsic factors

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Upadacitinib, at exposures (based on AUC) approximately 4 and 10 times the clinical dose of 15 mg, 2 and 5 times the clinical dose of 30 mg, and 1.6 and 4 times the clinical dose of 45 mg in male and female Sprague-Dawley rats, respectively, was not carcinogenic in a 2-year carcinogenicity study in Sprague-Dawley rats. Upadacitinib was not carcinogenic in a 26-week carcinogenicity study in CByB6F1-Tg(-HRAS)2Jic transgenic mice.

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

Upadacitinib had no effect on fertility in male or female rats at exposures up to approximately 15 and 31 times the maximum recommended human dose (MRHD) of 45 mg in males and females, respectively, on an AUC basis in a fertility and early embryonic development study. Dose-related increases in foetal resorptions associated with post-implantation losses in this fertility study in rats were attributed to the developmental/teratogenic effects of upadacitinib. No adverse effects were observed at exposures below clinical exposure (based on AUC). Post-implantation losses were observed at exposures 8 times the clinical exposure at the MRHD of 45 mg (based on AUC).

In animal embryo-foetal development studies, upadacitinib was teratogenic in both rats and rabbits. Upadacitinib resulted in increases in skeletal malformations in rats at 1.6, 0.8, and 0.6 times the clinical exposure (AUC-based) at the 15, 30, and 45 mg (MRHD) doses, respectively. In rabbits an increased incidence of cardiovascular malformations was observed at 15, 7.6, and 5.6 times the clinical exposure at the 15, 30, and 45 mg doses (AUC-based), respectively. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 1 times the MRHD of 45 mg resulted in no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on the offspring.

Following administration of upadacitinib to lactating rats, the concentrations of upadacitinib in milk over time generally paralleled those in plasma, with approximately 30-fold higher exposure in milk relative to maternal plasma. Approximately 97% of upadacitinib-related material in milk was the parent molecule, upadacitinib.

Administration of upadacitinib to juvenile Sprague-Dawley rats (from postnatal day 15 to 63) resulted in exposures and pharmacologic effects on the lymphoid system similar to those observed in adult rats. No adverse findings were observed in juvenile rats at exposures (AUC) approximately 9.4, 4.8, and 3.5 times the exposures at the clinical doses of 15, 30, and 45 mg, respectively (based on exposures in adult patients).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet contents:

Microcrystalline cellulose
Hypromellose

Mannitol
Tartaric acid
Silica, colloidal anhydrous
Magnesium stearate

Film coating:

Poly(vinyl alcohol)
Macrogol
Talc
Titanium dioxide (E171)
Iron oxide black (E172) (15 mg strength only)
Iron oxide red (E172)
Iron oxide yellow (E172) (45 mg strength only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to expiry date printed on the packaging.

6.4 Special precautions for storage

Store at or below 30°C.

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

6.5 Nature and contents of container

RINVOQ 15 mg extended-release tablets

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in packs containing 28 extended-release tablets.

RINVOQ 30 mg extended-release tablets

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in packs containing 28 extended-release tablets.

RINVOQ 45 mg extended-release tablets

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in packs containing 28 extended-release tablets.

Not all presentations may be available locally.

6.6 Special precautions for disposal

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

7. PRODUCT OWNER

AbbVie Inc., North Chicago, IL 60064, USA