

# NEW ZEALAND DATA SHEET

## 1 RINVOQ® UPADACITINIB 15 MG MODIFIED RELEASE TABLETS

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib, a JAK inhibitor.

The tablets do not contain gluten or lactose.

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

## 3 PHARMACEUTICAL FORM

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Rheumatoid Arthritis

RINVOQ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis.

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

#### Atopic Dermatitis

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

#### Psoriatic arthritis

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

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

### Ankylosing spondylitis

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

## **4.2 Dose and method of administration**

RINVOQ tablets should be taken orally with or without food.

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

### Rheumatoid Arthritis

The recommended dose of RINVOQ is 15 mg once daily.

RINVOQ may be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs.

### Atopic Dermatitis

#### **Adults**

The recommended dose of RINVOQ is 15 mg or 30 mg once daily for adults. Consider dose selection based on individual patient presentation.

For patients  $\geq 65$  years of age, the recommended dose of RINVOQ is 15 mg once daily.

#### **Adolescents (from 12 to 17 years of age)**

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

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

#### **Concomitant Topical Therapies**

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

### Psoriatic arthritis

The recommended dose of RINVOQ is 15 mg once daily.

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

### Ankylosing Spondylitis

The recommended dose of RINVOQ is 15 mg once daily.

## Dose Initiation

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

## Missed Dose

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

## Dose interruption

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

**Table 1. Recommended Dose Interruptions for Laboratory Abnormalities**

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

## Dosing in Special Populations:

### Paediatric Use

#### Atopic Dermatitis

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

#### Rheumatoid Arthritis

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

### Use in the Elderly

No dose adjustment is required in patients aged 65 years and older.

### Use in Renal Impairment

No dose adjustment is required in patients with mild or, moderate renal impairment. The recommended dose is 15 mg once daily for patients with severe renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease. Haemodialysis is not expected to have a clinically relevant effect on upadacitinib plasma exposures due to the major contribution of non-renal clearance to upadacitinib overall elimination (see **5 PHARMACOLOGICAL PROPERTIES**).

### Use in Hepatic Impairment

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

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

### Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis (see **4.8 ADVERSE EFFECTS**). Among opportunistic infections, tuberculosis, multi-dermatomal herpes zoster, oral/oesophageal candidiasis, and cryptococcosis were reported with RINVOQ.

Avoid use of RINVOQ in patients with an active, serious infection, including localised infections. Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

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

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

### **Tuberculosis**

Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of RINVOQ in patients with previously untreated latent TB.

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

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

### **Viral Reactivation**

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see **4.8 ADVERSE EFFECTS**). The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

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

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

### **Vaccination**

No data are available on the response to vaccination with live vaccines in patients receiving RINVOQ. Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines (see **5 PHARMACOLOGICAL PROPERTIES** for data on inactivated pneumococcal 13-valent conjugate vaccine and concomitant use with RINVOQ).

### **Malignancy**

The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medications may increase the risk of malignancies including lymphoma. The effect of RINVOQ treatment on malignancies is not known.

Malignancies were observed in clinical studies of RINVOQ (see **4.8 ADVERSE EFFECTS**). Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing RINVOQ in patients who develop a malignancy.

### **Non-Melanoma Skin Cancer**

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

### **Embryo-Foetal Toxicity**

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

### **Venous Thromboembolism**

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including RINVOQ. If clinical features of DVT/PE occur, patients should be evaluated promptly, followed by appropriate treatment.

## **Immunosuppressive medicinal products**

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

## **Use in the Elderly**

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

Of the 2485 patients treated in the atopic dermatitis Phase 3 clinical studies, 115 were 65 years of age or older. In the elderly, a higher rate of overall adverse events was observed compared to younger patients and in the RINVOQ 30 mg dose group compared to the 15 mg dose group.

## **Paediatric use**

### ***Atopic Dermatitis***

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

### ***Rheumatoid Arthritis***

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

## **Effects on Laboratory Tests**

### Neutropenia

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

### Lymphopenia

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

### Anaemia

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

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

Evaluate at baseline and thereafter according to routine patient management. Treatment should not be initiated or should be temporarily interrupted in patients who meet the criteria described in Table 1 (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

#### Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see **4.8 ADVERSE EFFECTS**). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

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

#### Liver Enzyme Elevations

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

Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

### **4.5 Interactions with other medicines and other forms of interactions**

#### **Strong CYP3A4 Inhibitors**

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole) (see **5 PHARMACOLOGICAL PROPERTIES**). RINVOQ 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. RINVOQ 30 mg once daily dose is not recommended for patients receiving chronic treatment with strong CYP3A4 inhibitors.



## Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampicin), which may lead to reduced therapeutic effect of RINVOQ (see **5 PHARMACOLOGICAL PROPERTIES**). Patients should be monitored for changes in disease activity if RINVOQ is co-administered with strong CYP3A4 inducers.

## Potential for Other Drugs to Affect the Pharmacokinetics of Upadacitinib

Upadacitinib is metabolised *in vitro* by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 2.

**Table 2. Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs**

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (90% CI) <sup>a</sup>		Clinical Impact
				C <sub>max</sub>	AUC	
Ketoconazole	400 mg once daily x 6 days	3 mg single dose <sup>b</sup>	11	1.70 (1.55-1.89)	1.75 (1.62-1.88)	RINVOQ 15 mg once daily is the recommended dose. Use with caution if used chronically.
Rifampicin	600 mg once daily x 9 days	12 mg single dose <sup>b</sup>	12	0.49 (0.44-0.55)	0.39 (0.37-0.42)	May decrease efficacy

CI: Confidence interval  
<sup>a</sup> Ratios for C<sub>max</sub> and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.  
<sup>b</sup> Upadacitinib was administered as an immediate-release formulation.

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

## Potential for Upadacitinib to Affect the Pharmacokinetics of Other Drugs

The effect of upadacitinib on plasma exposures of other drugs is provided in Table 3.

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

				Ratio (90% CI) <sup>a</sup>		
Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	C <sub>max</sub>	AUC	Clinical Impact
Midazolam	5 mg single dose	30 mg once daily x 10 days	20	0.74 (0.68-0.80)	0.74 (0.68-0.80)	No dose adjustment
Rosuvastatin	5 mg single dose	30 mg once daily x 10 days	12	0.77 (0.63-0.94)	0.67 (0.56-0.82)	No dose adjustment
Atorvastatin	10 mg single dose	30 mg once daily x 10 days	24	0.88 (0.79-0.97)	0.77 (0.70-0.85)	No dose adjustment

CI: Confidence interval

<sup>a</sup> Ratios for C<sub>max</sub> and AUC compare co-administration of the medication with upadacitinib vs. administration of medication alone

Upadacitinib has no relevant effects on plasma exposures of ethinylloestradiol, levonorgestrel, methotrexate, or drugs that are substrates for metabolism by CYP1A2, CYP2B6, CYP2D6, CYP2C19, or CYP2C9.

## 4.6 Fertility, Pregnancy and Lactation

### Effects on Fertility

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

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study were attributed to the developmental/teratogenic effects of upadacitinib in rats.

### Use in Pregnancy (Pregnancy Category D)

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

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

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

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

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

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

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

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

### **Use in Lactation**

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

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

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

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Adverse effects (Undesirable effects)**

##### **Clinical trials experience**

###### Rheumatoid Arthritis

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

Three placebo-controlled studies were integrated (1035 patients on RINVOQ 15 mg once daily and 1042 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 12-14 weeks after treatment initiation.

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

**Table 4. Adverse Drug Reactions**

<b>System Organ Class</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>
<b>Infections and infestations</b>	Upper respiratory tract infections (URTI)*		Pneumonia Herpes zoster Herpes simplex** Oral candidiasis
<b>Blood and lymphatic system disorders</b>		Neutropenia	
<b>Metabolism and nutrition disorders</b>		Hypercholesterolaemia	Hypertriglyceridemia
<b>Respiratory, thoracic and mediastinal disorders</b>		Cough	
<b>Gastrointestinal disorders</b>		Nausea	
<b>General disorders and administration site conditions</b>		Pyrexia	
<b>Investigations</b>		Blood creatine phosphokinase (CPK) increased ALT increased AST increased Weight increased	
<p>* URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection</p> <p>** Herpes simplex includes oral herpes</p>			

## **Specific Adverse Reactions**

### ***Infections***

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

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

### ***Tuberculosis***

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

### ***Opportunistic Infections (excluding tuberculosis)***

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

### ***Malignancy***

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

### ***Gastrointestinal Perforations***

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

### ***Thrombosis***

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

### ***Hepatic transaminase elevations***

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

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

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

### ***Lipid elevations***

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

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

### ***Creatinine phosphokinase (CPK)***

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

### ***Neutropenia***

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

### ***Lymphopenia***

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

### ***Anaemia***

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

### **Atopic Dermatitis**

#### **Tabulated summary of adverse reactions**

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

Four global placebo-controlled studies (one Phase 2 study and three Phase 3 studies) were integrated (899 patients on RINVOQ 15 mg once daily, 906 patients on RINVOQ 30 mg once daily



and 902 patients on placebo) to evaluate the safety of RINVOQ 15 mg and 30 mg in comparison to placebo for up to 16 weeks after treatment initiation.

The frequency of adverse reactions listed below is defined using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  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) <sup>a</sup>	Herpes simplex <sup>b</sup> Herpes zoster Folliculitis influenza	Pneumonia Oral candidiasis
Blood and lymphatic system disorders		Neutropenia Anemia	
Metabolism and nutrition disorders			Hypercholesterolemia Hypertriglyceridemia
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea Abdominal pain <sup>c</sup>	
General disorders and administration site conditions		Pyrexia Fatigue	
Investigations		Blood creatine phosphokinase increased Weight increased	ALT increased AST increased
Skin and subcutaneous tissue disorders	Acne	Urticaria	
Nervous system disorders		Headache	
<sup>a</sup> 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 <sup>b</sup> Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes <sup>c</sup> Includes abdominal pain and abdominal pain upper			

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

## **Specific Adverse Reactions**

### ***Infections***

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

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

### ***Tuberculosis***

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

### ***Opportunistic Infections (excluding tuberculosis)***

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

The long-term rate of herpes zoster for the RINVOQ 15 mg and 30 mg groups was 3.8 and 5.3 events per 100 patient-years, respectively.

### ***Malignancy***

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

### ***Gastrointestinal Perforations***

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

### ***Thrombosis***

In placebo-controlled studies over 16 weeks, there were no venous thrombosis events (pulmonary embolism or deep vein thrombosis) in the RINVOQ 15 mg and 30 mg groups compared to 1 event (0.1%) in the placebo group. The long-term incidence rate of venous thrombosis for RINVOQ treatment across the AD clinical studies was <0.1 per 100 patient-years.

### ***Hepatic transaminase elevations***

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

### ***Lipid elevations***

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

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

Small increases in LDL cholesterol were observed after week 16.

### ***Creatine phosphokinase elevations***

In placebo-controlled studies, for up to 16 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations  $> 5$  x ULN were reported in 3.3%, 4.4% and 1.7% of patients over 16 weeks in the RINVOQ 15 mg, 30 mg and placebo groups, respectively. Most elevations  $> 5$  x ULN were transient and did not require treatment discontinuation.

### ***Neutropenia***

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

### ***Lymphopenia***

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

### ***Anaemia***

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

### ***Paediatric population***

A total of 343 adolescents aged 12 to 17 years weighing at least 40 kg with atopic dermatitis were treated in the Phase 3 studies. The safety profile for RINVOQ 15 mg was similar in adolescents and adults.

### ***Psoriatic arthritis***

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical studies representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the Phase 3 studies, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

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

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were >1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively, with placebo.

A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

### **Ankylosing Spondylitis**

A total of 182 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the clinical study representing 237.6 patient-years of exposure, of whom 160 were exposed to RINVOQ 15 mg for at least one year.

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

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 Overdose**

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

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

ATC code: L04AA44.

## **Mechanism of action**

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

Upadacitinib is a selective and reversible inhibitor of JAK1. Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 50–70-fold greater selectivity for JAK1 over JAK2 and >100-fold for JAK1 over JAK3. Atopic dermatitis pathogenesis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN- $\gamma$ ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signalling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus.

## **Pharmacodynamics**

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

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

### Lymphocytes

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

### Immunoglobulins

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

### High-Sensitivity (hs) CRP

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

### Cardiac Electrophysiology

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

### Vaccine Study

The influence of RINVOQ on the humoral response following the administration of inactivated pneumococcal 13-valent conjugate vaccine was evaluated in 111 patients with rheumatoid arthritis under stable treatment with 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 trials**

### Rheumatoid arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in five, Phase 3 randomised, double-blind, multicentre studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria (see Table 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.

**Table 6. Clinical Trial Summary**

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT EARLY	MTX-naïve <sup>a</sup>  (947)	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• MTX</li> </ul> Monotherapy	Primary Endpoint: <ul style="list-style-type: none"> <li>• ACR 50 at Week 12</li> </ul>
			Key Secondary Endpoints: <ul style="list-style-type: none"> <li>• Low Disease Activity (DAS28-CRP <math>\leq</math> 3.2) at Week 12</li> <li>• Clinical Remission (DAS28-CRP <math>&lt;</math>2.6) at Week 24</li> <li>• <math>\Delta</math> Physical Function (HAQ-DI) at Week 12</li> <li>• Radiographic progression (<math>\Delta</math>mTSS) at Week 24</li> <li>• SF-36 PCS</li> </ul>
SELECT MONOTHERAPY	MTX-IR <sup>b</sup>  (648)	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• MTX</li> </ul> Monotherapy	Primary Endpoint: <ul style="list-style-type: none"> <li>• ACR20 at Week 14</li> </ul>
			Key Secondary Endpoints: <ul style="list-style-type: none"> <li>• Low Disease Activity (DAS28-CRP <math>\leq</math> 3.2) at Week 14</li> <li>• Clinical Remission (DAS 28-CRP <math>&lt;</math>2.6) at Week 14</li> <li>• <math>\Delta</math> Physical Function (HAQ-DI) at Week 14</li> <li>• SF-36 PCS</li> <li>• Morning stiffness</li> </ul>
SELECT NEXT	csDMARD IR <sup>c</sup>  (661)	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• Placebo</li> </ul> On background csDMARDs	Primary Endpoint: <ul style="list-style-type: none"> <li>• ACR20 at Week 12</li> </ul>
			Key Secondary Endpoints: <ul style="list-style-type: none"> <li>• Clinical Remission (DAS28- CRP <math>&lt;</math>2.6) at Week 12</li> <li>• <math>\Delta</math> Physical Function HAQ-DI at Week 12</li> <li>• Low Disease Activity (DAS28-CRP <math>\leq</math> 3.2) at Week 12</li> <li>• SF-36 PCS</li> <li>• Morning stiffness</li> <li>• FACIT-F</li> </ul>
SELECT COMPARE	MTX-IR <sup>d</sup>  (1629)	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Placebo</li> <li>• Adalimumab 40 mg</li> </ul> On background MTX	Primary Endpoint: <ul style="list-style-type: none"> <li>• ACR20 at Week 12</li> </ul>
			Key Secondary Endpoints: <ul style="list-style-type: none"> <li>• Low Disease Activity (DAS28-CRP <math>\leq</math>3.2) at Week 12</li> <li>• Clinical Remission (DAS28-CRP <math>&lt;</math>2.6) at Week 12</li> <li>• ACR50 vs adalimumab at Week 12</li> <li>• <math>\Delta</math> Physical Function</li> </ul>



			(HAQ-DI) at Week 12 • Radiographic progression ( $\Delta$ mTSS) at Week 26 • SF-36 PCS • Morning stiffness • FACIT-F
SELECT BEYOND	bDMARD- IR <sup>e</sup>  (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Primary Endpoint: • ACR20 at Week 12
		On background csDMARDs	Key Secondary Endpoint: • Low Disease Activity (DAS28-CRP $\leq$ 3.2) at Week 12 • $\Delta$ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS

**Abbreviations:**

ACR20 (or 50) = American College of Rheumatology  $\geq$ 20% (or  $\geq$ 50%) improvement

bDMARD = biologic disease-modifying anti-rheumatic drug

CR = Clinical Response

CRP = C-Reactive Protein

DAS28 = Disease Activity Score 28 joints

FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue

mTSS = modified Total Sharp Score

csDMARD = conventional synthetic disease-modifying anti-rheumatic drug

HAQ-DI = Health Assessment Questionnaire Disability Index

IR = inadequate responder

MTX = methotrexate

SF-36 = Short Form (36) Health Survey

PCS = Physical Component Summary

<sup>a</sup> Patients were naïve to MTX or received no more than 3 weekly MTX doses

<sup>b</sup> Patients had inadequate response to MTX

<sup>c</sup> 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

<sup>d</sup> 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

<sup>e</sup> Patients who had an inadequate response or intolerance to at least one bDMARD

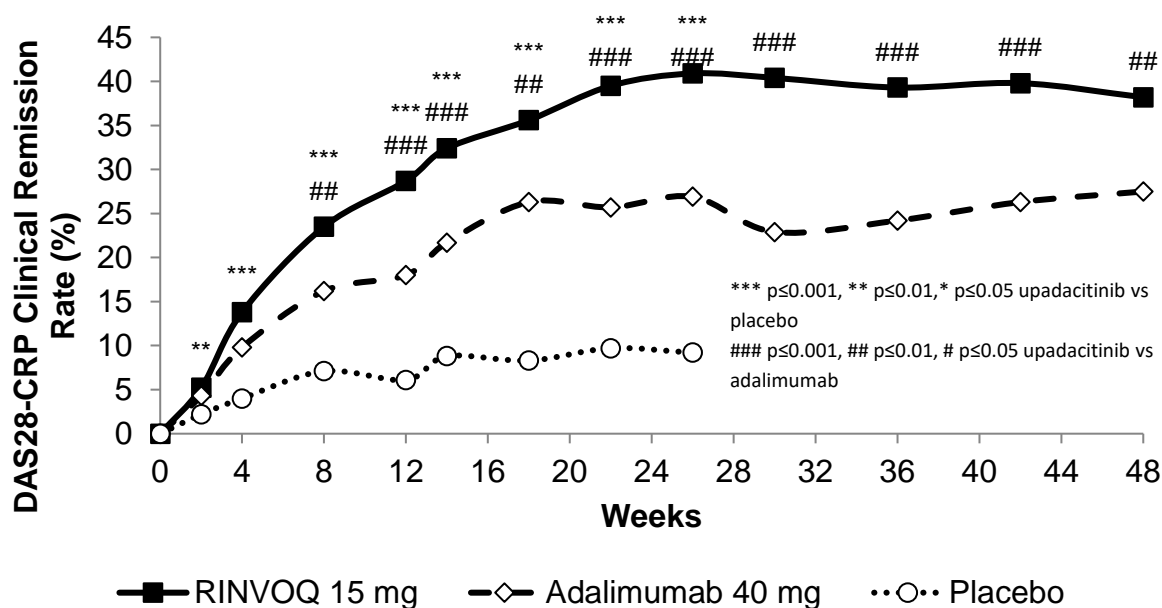
## Clinical Response

### ***Remission and low disease activity***

In all studies, a significantly higher proportion of patients treated with RINVOQ 15 mg achieved both low disease activity (DAS28-CRP  $\leq$ 3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX, or adalimumab (Table 6). Compared to adalimumab, significantly higher responses were achieved as early as Week 8 and maintained through Week 48 (Figure 1). Significantly higher responses were also observed for other disease activity outcomes including CDAI  $\leq$ 2.8, SDAI  $\leq$ 3.3, and Boolean remission. Overall, both low disease activity and clinical remission rates were

consistent across patient populations, with or without MTX, and were maintained through 3 years based on available long-term extension study results.

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



### ACR Response

In all studies, significantly more patients treated with RINVOQ 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo or MTX except for ACR70 in SELECT-BEYOND (Table 7). Time to onset of efficacy was rapid across measures with significantly greater responses seen as early as Week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained through 3 years based on available long-term extension study results. The percentage of patients who achieved ACR20/50/70 responses at each visit in SELECT-COMPARE are shown in Figure 2, Figure 3 and Figure 4.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in significant improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP, compared to placebo or MTX monotherapy (Table 8).

In SELECT-COMPARE, a significantly higher proportion of patients treated with RINVOQ 15 mg achieved ACR20/50/70 at Weeks 12 through 48 compared to adalimumab. In addition, greater improvements were observed for individual ACR components (Table 7).

Figure 2. Percent of Patients Achieving ACR20 in SELECT COMPARE

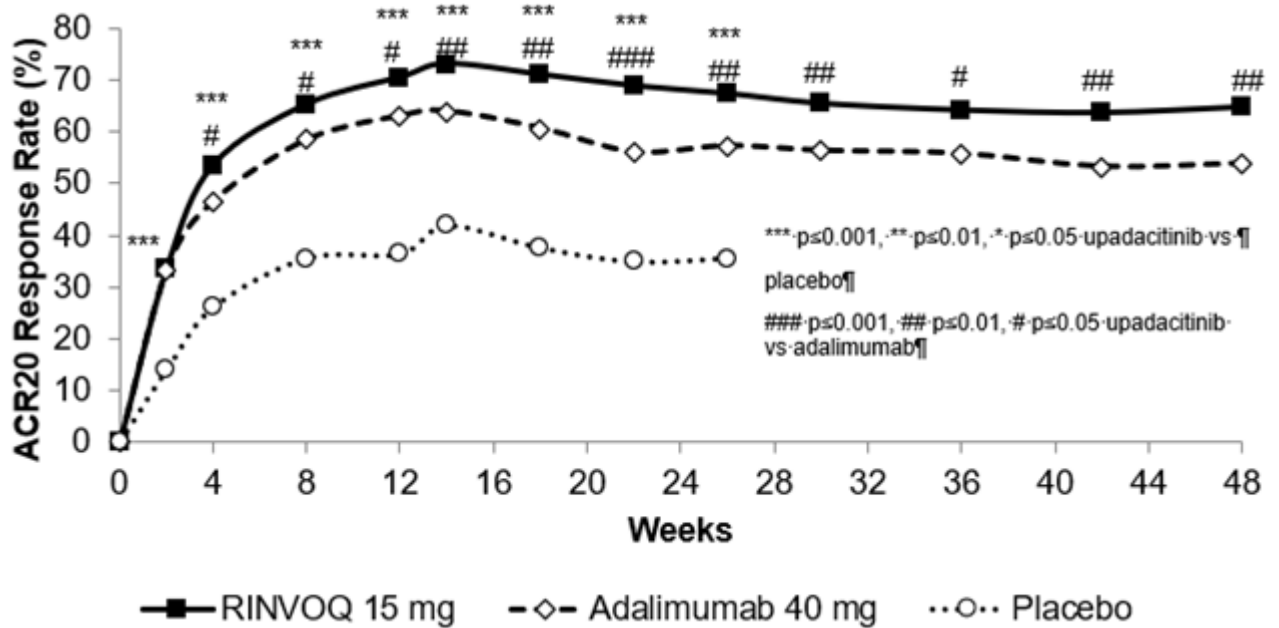


Figure 3. Percent of Patients Achieving ACR50 in SELECT COMPARE

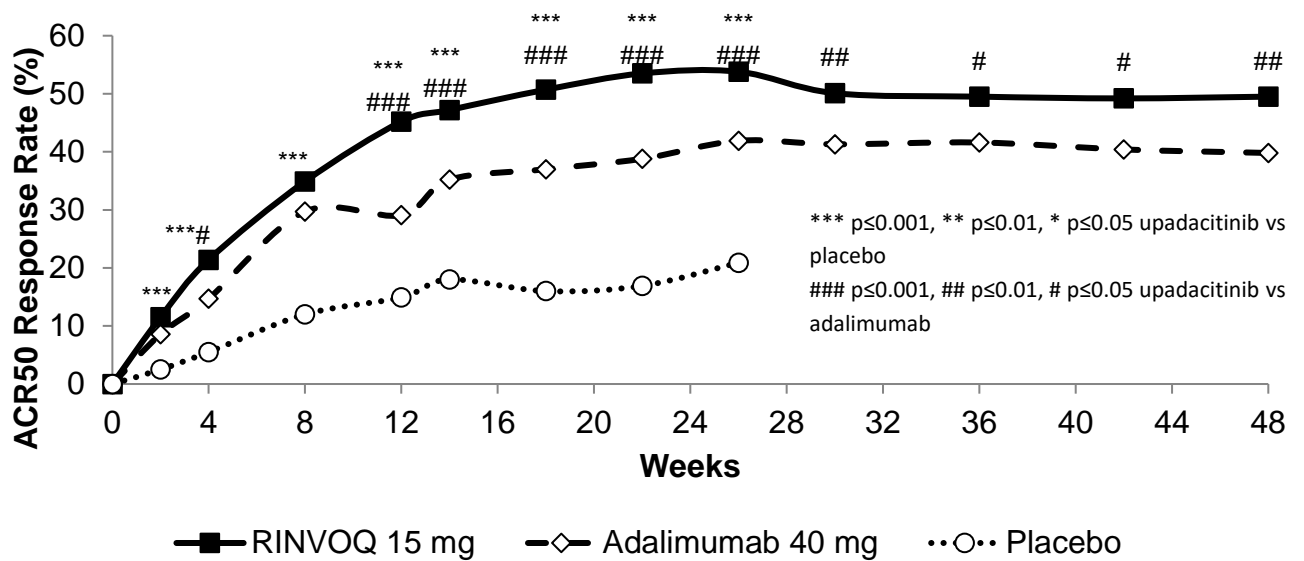
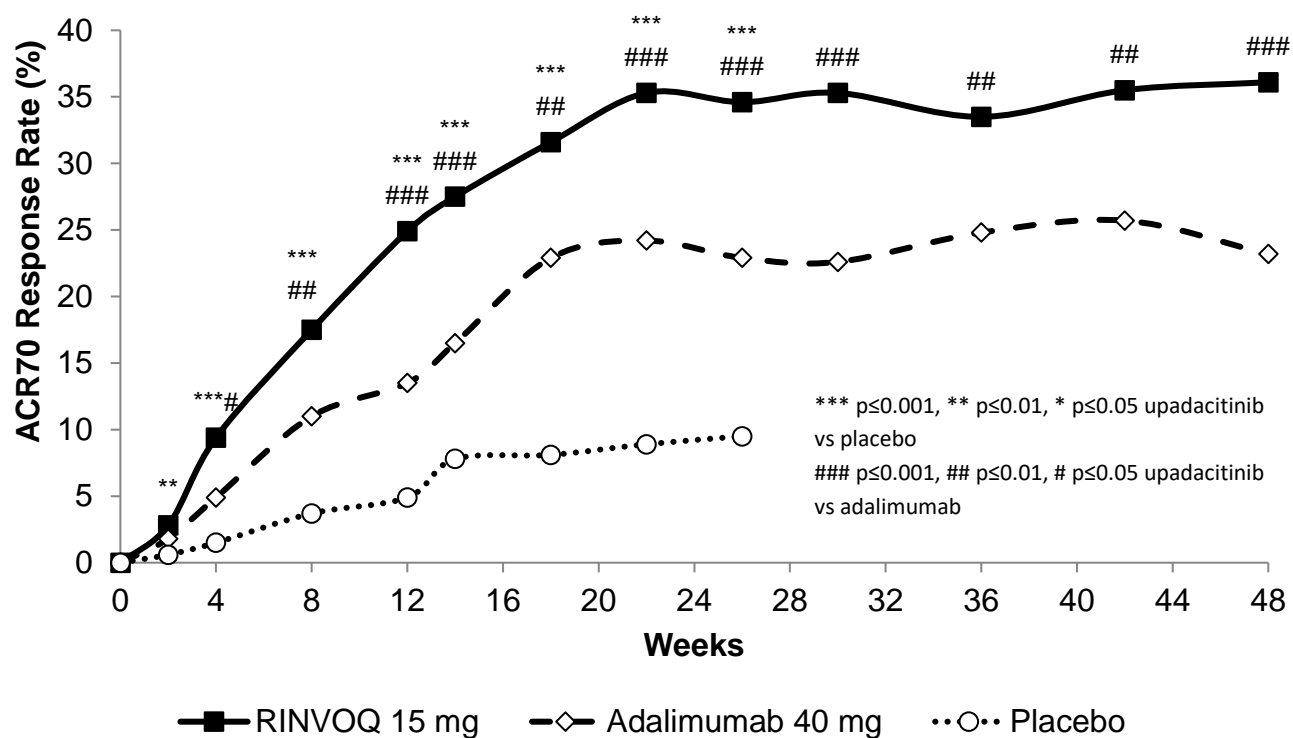


Figure 4. Percent of Patients Achieving ACR70 in SELECT COMPARE



**Table 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 15mg	MTX	UPA 15mg	PBO	UPA 15mg	PBO	UPA 15mg	ADA 40mg	PBO	UPA 15mg
N	314	317	216	217	221	221	651	651	327	169	164
Week											
<b>ACR20 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	54	76 <sup>e</sup>	41	68 <sup>e</sup>	36	64 <sup>e</sup>	36	71 <sup>e,j</sup>	63	28	65 <sup>e</sup>
24 <sup>c</sup> /26 <sup>d</sup>	59	79 <sup>e</sup>					36	67 <sup>e,i</sup>	57		
48	57	74 <sup>e</sup>						65 <sup>i</sup>	54		
<b>ACR50 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	28	52 <sup>e</sup>	15	42 <sup>e</sup>	15	38 <sup>e</sup>	15	45 <sup>e,h</sup>	29	12	34 <sup>e</sup>
24 <sup>c</sup> /26 <sup>d</sup>	33	60 <sup>e</sup>					21	54 <sup>e,h</sup>	42		
48	43	63 <sup>e</sup>						49 <sup>i</sup>	40		
<b>ACR70 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	14	32 <sup>e</sup>	3	23 <sup>e</sup>	6	21 <sup>e</sup>	5	25 <sup>e,h</sup>	13	7	12
24 <sup>c</sup> /26 <sup>d</sup>	18	44 <sup>e</sup>					10	35 <sup>e,h</sup>	23		
48	29	51 <sup>e</sup>						36 <sup>h</sup>	23		
<b>LDA DAS28-CRP ≤3.2 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	28	53 <sup>e</sup>	19	45 <sup>e</sup>	17	48 <sup>e</sup>	14	45 <sup>e,h</sup>	29	14	43 <sup>e</sup>
24 <sup>c</sup> /26 <sup>d</sup>	32	60 <sup>e</sup>					18	55 <sup>e,h</sup>	39		
48	39	59 <sup>e</sup>						50 <sup>h</sup>	35		
<b>CR DAS28-CRP &lt;2.6 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	14	36 <sup>e</sup>	8	28 <sup>e</sup>	10	31 <sup>e</sup>	6	29 <sup>e,h</sup>	18	9	29 <sup>e</sup>
24 <sup>c</sup> /26 <sup>d</sup>	18	48 <sup>e</sup>					9	41 <sup>e,h</sup>	27		
48	29	49 <sup>e</sup>						38 <sup>i</sup>	28		
<b>SDAI ≤3.3 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	6	16 <sup>e</sup>	1	14 <sup>e</sup>	3	10 <sup>f</sup>	3	12 <sup>e,j</sup>	7	5	9
24 <sup>c</sup> /26 <sup>d</sup>	9	28 <sup>e</sup>					5	24 <sup>e,h</sup>	14		
48	16	32 <sup>e</sup>						25 <sup>i</sup>	17		
<b>CDAI ≤2.8 (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	6	16 <sup>e</sup>	1	13 <sup>e</sup>	3	9 <sup>f</sup>	3	13 <sup>e,i</sup>	8	5	8
24 <sup>c</sup> /26 <sup>d</sup>	11	28 <sup>e</sup>					6	23 <sup>e,h</sup>	14		
48	17	32 <sup>e</sup>						25 <sup>i</sup>	17		
<b>Boolean Remission (% of patients)</b>											
12 <sup>a</sup> /14 <sup>b</sup>	6	13 <sup>f</sup>	1	9 <sup>e</sup>	4	10 <sup>f</sup>	2	10 <sup>e,i</sup>	4	2	7 <sup>g</sup>
24 <sup>c</sup> /26 <sup>d</sup>	7	24 <sup>e</sup>					4	18 <sup>e,h</sup>	10		
48	13	28 <sup>e</sup>						21 <sup>i</sup>	15		

Study	SELECT EARLY MTX-Naïve	SELECT MONO MTX-IR	SELECT NEXT csDMARD-IR	SELECT COMPARE MTX-IR	SELECT BEYOND bDMARD-IR
<p><b>Abbreviations:</b> ACR20 (or 50 or 70) = American College of Rheumatology <math>\geq 20\%</math> (or <math>\geq 50\%</math> or <math>\geq 70\%</math>) improvement; ADA = adalimumab; bDMARD = biologic disease modifying anti-rheumatic drug; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = c-reactive protein, csDMARD = conventional synthetic disease modifying anti-rheumatic drug; DAS28 = Disease Activity Score 28 joints; IR = inadequate responder; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; SDAI = Simple Disease Activity Index; UPA= upadacitinib</p> <p><sup>a</sup> SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND</p> <p><sup>b</sup> SELECT-MONOTHERAPY</p> <p><sup>c</sup> SELECT-EARLY</p> <p><sup>d</sup> SELECT-COMPARE</p> <p><sup>e</sup> <math>p \leq 0.001</math> upadacitinib vs placebo or MTX comparison</p> <p><sup>f</sup> <math>p \leq 0.01</math> upadacitinib vs placebo or MTX comparison</p> <p><sup>g</sup> <math>p &lt; 0.05</math> upadacitinib vs placebo or MTX comparison</p> <p><sup>h</sup> <math>p \leq 0.001</math> upadacitinib vs adalimumab comparison</p> <p><sup>i</sup> <math>p \leq 0.01</math> upadacitinib vs adalimumab comparison</p> <p><sup>j</sup> <math>p &lt; 0.05</math> upadacitinib vs adalimumab comparison</p>					

**Table 8: Components of ACR Response (mean change from baseline)<sup>a</sup>**

Study	SELECT EARLY MTX-Naive		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND bDMARD-IR	
	MTX	UPA 15mg	MTX	UPA 15mg	PB O	UPA 15mg	PBO	UPA 15mg	ADA 40mg	PBO	UPA 15mg
N	314	317	216	217	221	221	651	651	327	169	164
<b>Week</b>											
<b>Number of tender joints (0-68)</b>											
12 <sup>b</sup> /14 <sup>c</sup>	-13	-17 <sup>h</sup>	-11	-15 <sup>h</sup>	-8	-14 <sup>h</sup>	-10	-16 <sup>h,k</sup>	-14	-8	-16 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-16	-19 <sup>h</sup>					-9	-18 <sup>h,j</sup>	-15		
<b>Number of swollen joints (0-66)</b>											
12 <sup>b</sup> /14 <sup>c</sup>	-10	-12 <sup>h</sup>	-8	-11 <sup>h</sup>	-6	-9 <sup>h</sup>	-7	-11 <sup>h</sup>	-10	-6	-11 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-12	-14					-6	-12 <sup>h</sup>	-11		
<b>Pain<sup>f</sup></b>											
12 <sup>b</sup> /14 <sup>c</sup>	-25	-36 <sup>h</sup>	-14	-26 <sup>h</sup>	-10	-30 <sup>h</sup>	-15	-32 <sup>h,i</sup>	-25	-10	-26 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-28	-40 <sup>h</sup>					-19	-37 <sup>h,j</sup>	-32		
<b>Patient global assessment<sup>f</sup></b>											
12 <sup>b</sup> /14 <sup>c</sup>	-25	-35 <sup>h</sup>	-11	-23 <sup>h</sup>	-10	-30 <sup>h</sup>	-15	-30 <sup>h,i</sup>	-24	-10	-26 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-28	-39 <sup>h</sup>					-18	-36 <sup>h,j</sup>	-30		
<b>Disability Index (HAQ-DI)<sup>g</sup></b>											
12 <sup>b</sup> /14 <sup>c</sup>	-0.5	-0.8 <sup>h</sup>	-0.3	-0.7 <sup>h</sup>	-0.3	-0.6 <sup>h</sup>	-0.3	-0.6 <sup>h,j</sup>	-0.5	-0.2	-0.4 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-0.6	-0.9 <sup>h</sup>					-0.3	-0.7 <sup>h,j</sup>	-0.6		
<b>Physician global assessment<sup>f</sup></b>											
12 <sup>b</sup> /14 <sup>c</sup>	-35	-46 <sup>h</sup>	-26	-40 <sup>h</sup>	-23	-38 <sup>h</sup>	-25	-39 <sup>h</sup>	-36	-26	-39 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-45	-50 <sup>h</sup>					-27	-45 <sup>h,j</sup>	-41		
<b>CRP (mg/L)</b>											
12 <sup>b</sup> /14 <sup>c</sup>	-10.6	-17.5 <sup>h</sup>	-1.1	-10.2 <sup>h</sup>	-0.4	-10.1 <sup>h</sup>	-1.7	-12.5 <sup>h,j</sup>	-9.2	-1.1	-11.0 <sup>h</sup>
24 <sup>d</sup> /26 <sup>e</sup>	-11.6	-18.4 <sup>h</sup>					-1.5	-13.5 <sup>h,j</sup>	-10.3		
<p><b>Abbreviations:</b>            ACR = American College of Rheumatology            ADA = adalimumab            bDMARD = biologic disease-modifying anti rheumatic drug            CRP = c-reactive protein            csDMARD = conventional synthetic disease-modifying anti-rheumatic drug            HAQ-DI = Health Assessment Questionnaire Disability Index            IR = inadequate responder            MTX = methotrexate            PBO = placebo            UPA = upadacitinib  <sup>a</sup> Data shown are mean  <sup>b</sup> SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND  <sup>c</sup> SELECT-MONOTHERAPY  <sup>d</sup> SELECT-EARLY  <sup>e</sup> SELECT-COMPARE  <sup>f</sup> Visual analog scale: 0 = best, 100 = worst</p>											

<sup>g</sup> Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.  
<sup>h</sup> p≤0.001 upadacitinib vs placebo or MTX comparison  
<sup>i</sup> p≤0.001 upadacitinib vs adalimumab comparison  
<sup>j</sup> p≤0.01 upadacitinib vs adalimumab comparison  
<sup>k</sup> p<0.05 upadacitinib vs adalimumab comparison

## Radiographic Response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score, and joint space narrowing score at Weeks 26 and 48 (SELECT-COMPARE) and Week 24 (SELECT-EARLY).

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Weeks 26 and 48 in SELECT-COMPARE and as monotherapy compared to MTX at Week 24 in SELECT-EARLY (Table 9). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with RINVOQ 15 mg compared to placebo at Weeks 26 and 48 (SELECT-COMPARE) and compared to MTX at Week 24 (SELECT-EARLY). Inhibition of progression of structural joint damage was maintained through Week 96 in both studies for patients receiving RINVOQ 15 mg.



**Table 9: Radiographic Changes**

Study	SELECT EARLY MTX-Naïve		SELECT COMPARE MTX-IR		
	MTX	UPA 15 mg	PBO <sup>a</sup>	UPA 15mg	ADA 40mg
<b>Modified Total Sharps Score, mean change from baseline</b>					
Week 24 <sup>b</sup> /26 <sup>c</sup>	0.7	0.1 <sup>f</sup>	0.9	0.2 <sup>e</sup>	0.1
Week 48			1.7	0.3 <sup>e</sup>	0.4
<b>Erosion Score, mean change from baseline</b>					
Week 24 <sup>b</sup> /26 <sup>c</sup>	0.3	0.1 <sup>e</sup>	0.4	0 <sup>e</sup>	0
Week 48			0.8	0.1 <sup>e</sup>	0.2
<b>Joint Space Narrowing Score, mean change from baseline</b>					
Week 24 <sup>b</sup> /26 <sup>c</sup>	0.3	0.1 <sup>g</sup>	0.6	0.2 <sup>e</sup>	0.1
Week 48			0.8	0.2 <sup>e</sup>	0.2
<b>Proportion of patients with no radiographic progression<sup>d</sup></b>					
Week 24 <sup>b</sup> /26 <sup>c</sup>	77.7	87.5 <sup>f</sup>	76.0	83.5 <sup>f</sup>	86.8
Week 48			74.1	86.4 <sup>e</sup>	87.9
Abbreviations: ADA = adalimumab IR = inadequate responder MTX = methotrexate PBO = placebo UPA= upadacitinib <sup>a</sup> All placebo data at Week 48 derived using linear extrapolation <sup>b</sup> SELECT-EARLY <sup>c</sup> SELECT-COMPARE <sup>d</sup> No progression defined as mTSS change ≤0. <sup>e</sup> p≤0.001 upadacitinib vs placebo or MTX comparison <sup>f</sup> p≤0.01 upadacitinib vs placebo or MTX comparison <sup>g</sup> p<0.05 upadacitinib vs placebo or MTX comparison					

### Physical Function Response and Health-Related Outcomes

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

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

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

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

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

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

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

### Atopic Dermatitis

The efficacy and safety of RINVOQ 15 mg and 30 mg once daily was assessed in three Phase 3 randomized, double-blind, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 2584 patients (12 years of age and older) (Table 10). 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  $\geq 3$  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  $\geq 16$  (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  $\geq 10\%$ , and weekly average Worst Pruritus Numerical Rating Scale (NRS)  $\geq 4$ .

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 10. Clinical Trial Summary**

Study Name	Treatment Arms	Key Outcome Measures
MEASURE UP 1 and MEASURE UP 2	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• Placebo</li> </ul>	<p>Co-Primary Endpoints at Week 16:</p> <ul style="list-style-type: none"> <li>• EASI 75</li> <li>• vIGA-AD 0/1</li> </ul> <hr/> <p>Key Secondary Endpoints (at Week 16 except where noted)</p> <ul style="list-style-type: none"> <li>• EASI 90/100</li> <li>• EASI 75 at Week 2</li> <li>• % change in EASI</li> <li>• % change in SCORAD</li> <li>• Worst Pruritus NRS improvement <math>\geq 4</math> at Week 1 and 16</li> <li>• Worst Pruritus NRS improvement <math>\geq 4</math> at Day 2 (30 mg), Day 3 (15 mg)</li> <li>• % change in Worst Pruritus NRS</li> <li>• EASI increase <math>\geq 6.6</math> points (flare) during double-blind period</li> <li>• ADerm-SS TSS-7 improvement <math>\geq 28</math></li> <li>• ADerm-SS Skin Pain improvement <math>\geq 4</math></li> <li>• ADerm-IS Sleep improvement <math>\geq 12</math></li> <li>• ADerm-IS Emotional State improvement <math>\geq 11</math></li> <li>• ADerm-IS Daily Activities improvement <math>\geq 14</math></li> <li>• POEM improvement <math>\geq 4</math></li> <li>• HADS-A <math>&lt; 8</math> and HADS-D <math>&lt; 8</math></li> <li>• DLQI 0/1</li> <li>• DLQI improvement <math>\geq 4</math></li> </ul>
AD UP	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• Placebo</li> </ul>	<p>Co-Primary Endpoints at Week 16:</p> <ul style="list-style-type: none"> <li>• EASI 75</li> <li>• vIGA-AD 0/1</li> </ul> <hr/> <p>Key Secondary Endpoints (at Week 16 except where noted)</p> <ul style="list-style-type: none"> <li>• EASI 75 at Week 2 and 4</li> <li>• EASI 90 at Week 4 and 16</li> <li>• EASI 100 (30 mg)</li> <li>• % change in EASI</li> <li>• Worst Pruritus NRS improvement <math>\geq 4</math> at Week 1, 4 and 16</li> <li>• % change in Worst Pruritus NRS</li> </ul>
<p>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</p>		

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 11). 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  $\geq 4$ -point reduction in the Worst Pruritus NRS) compared to placebo at week 16. Rapid improvement in itch (defined as a  $\geq 4$ -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  $\geq 6.6$ ), during the initial 16 weeks of treatment compared to placebo ( $p < 0.001$ ).

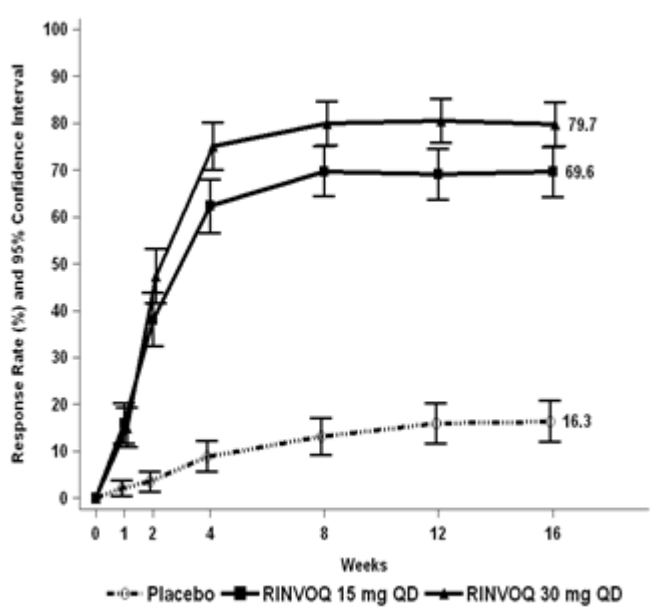
Figure 5 and Figure 6 show proportion of patients achieving an EASI 75 response and the proportion of patients with  $\geq 4$ -point improvement in the Worst Pruritus NRS, respectively up to week 16.

**Table 11. Efficacy results of RINVOQ monotherapy studies at week 16**

Study	MEASURE UP 1			MEASURE UP 2		
	PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg
Number of subjects randomized	281	281	285	278	276	282
<b>% responders</b>						
vIGA-AD 0/1 <sup>a,b</sup>	8.4%	48.1% <sup>f</sup>	62.0% <sup>f</sup>	4.7%	38.8% <sup>f</sup>	52.0% <sup>f</sup>
EASI 75 <sup>a</sup>	16.3%	69.6% <sup>f</sup>	79.7% <sup>f</sup>	13.3%	60.1% <sup>f</sup>	72.9% <sup>f</sup>
EASI 90 <sup>a</sup>	8.1%	53.1% <sup>f</sup>	65.8% <sup>f</sup>	5.4%	42.4% <sup>f</sup>	58.5% <sup>f</sup>
EASI 100 <sup>a</sup>	1.8 %	16.7% <sup>f</sup>	27.0% <sup>f</sup>	0.7%	14.1% <sup>f</sup>	18.8% <sup>f</sup>
Worst Pruritus NRS <sup>c</sup> (≥ 4-point improvement)	11.8% N=272	52.2% <sup>f</sup> N=274	60.0% <sup>f</sup> N=280	9.1% N=274	41.9% <sup>f</sup> N=270	59.6% <sup>f</sup> N=280
Worst Pruritus NRS 0 or 1 <sup>d</sup>	5.5% N=275	36.6% <sup>g</sup> N=279	47.5% <sup>g</sup> N=282	4.3% N=277	26.9% <sup>g</sup> N=275	44.1% <sup>g</sup> N=281
Mean percent change (SE) <sup>e</sup>						
EASI	-40.7% (2.28)	-80.2% <sup>f</sup> (1.91)	-87.7% <sup>f</sup> (1.87)	-34.5% (2.59)	-74.1% <sup>f</sup> (2.20)	-84.7% <sup>f</sup> (2.18)
SCORAD	-32.7% (2.33)	-65.7% <sup>f</sup> (1.78)	-73.1% <sup>f</sup> (1.73)	-28.4% (2.50)	-57.9% <sup>f</sup> (2.01)	-68.4% <sup>f</sup> (2.04)
Worst Pruritus NRS	-26.1% (5.41)	-62.8% <sup>f</sup> (4.49)	-72.0% <sup>f</sup> (4.41)	-17.0% (2.73)	-51.2% <sup>f</sup> (2.34)	-66.5% <sup>f</sup> (2.31)
Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo						
<sup>a</sup> Based on number of subjects randomized						
<sup>b</sup> 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						
<sup>c</sup> N = number of patients whose baseline Worst Pruritus NRS is ≥ 4						
<sup>d</sup> N = number of patients whose baseline Worst Pruritus NRS is > 1						
<sup>e</sup> % change = least squares mean percent change relative to baseline						
<sup>f</sup> multiplicity-controlled p < 0.001 upadacitinib vs placebo comparison						
<sup>g</sup> 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

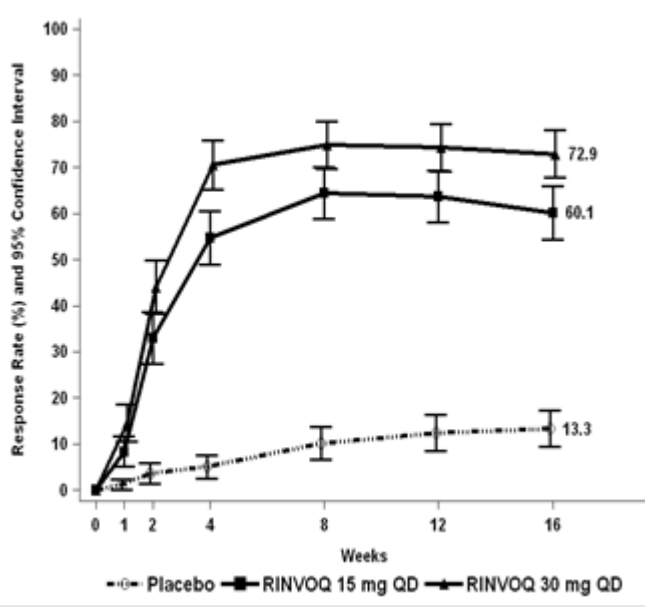
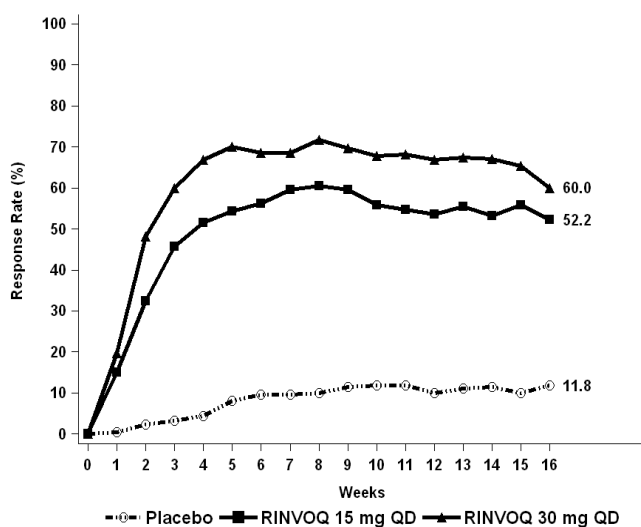
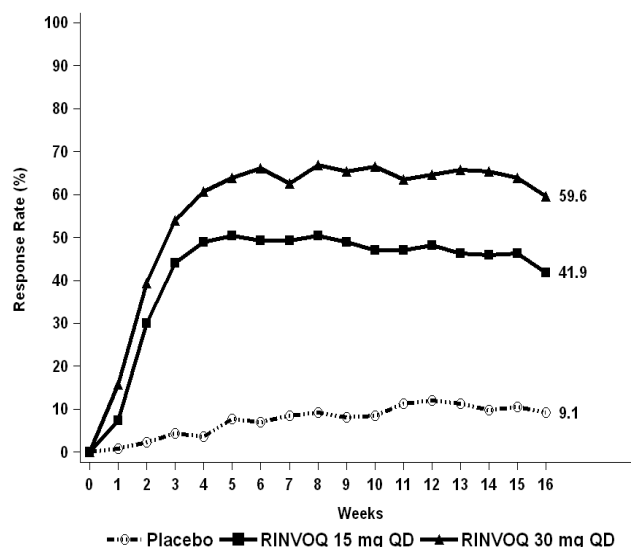


Figure 6. Proportion of patients with  $\geq 4$ -point improvement in the Worst Pruritus NRS in monotherapy studies

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 12). 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  $\geq 4$  point reduction in the Worst Pruritus NRS) compared to placebo + TCS at week 16. A rapid improvement in itch (defined as a  $\geq 4$  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  $\geq 4$ -point improvement in the Worst Pruritus NRS, respectively up to week 16.



**Table 12. 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
<b>% responders</b>			
vIGA-AD 0/1 <sup>a,b</sup>	10.9%	39.6% <sup>f</sup>	58.6% <sup>f</sup>
EASI 75 <sup>a</sup>	26.4%	64.6% <sup>f</sup>	77.1% <sup>f</sup>
EASI 90 <sup>a</sup>	13.2%	42.8% <sup>f</sup>	63.1% <sup>f</sup>
EASI 100 <sup>a</sup>	1.3%	12.0% <sup>g</sup>	22.6% <sup>f</sup>
Worst Pruritus NRS <sup>c</sup> (≥ 4-point improvement)	15.0% N=294	51.7% <sup>f</sup> N=288	63.9% <sup>f</sup> N=291
Worst Pruritus NRS 0 or 1 <sup>d</sup>	7.3% N=300	33.1% <sup>g</sup> N=296	43.0% <sup>g</sup> N=293
<b>Mean percent change (SE)<sup>e</sup></b>			
EASI	-45.9% (2.16)	-78.0% <sup>f</sup> (1.98)	-87.3% <sup>f</sup> (1.98)
SCORAD	-33.6% (1.90)	-61.2% <sup>g</sup> (1.70)	-71.0% <sup>g</sup> (1.71)
Worst Pruritus NRS	-25.1% (3.35)	-58.1% <sup>f</sup> (3.11)	-66.9% <sup>f</sup> (3.12)
Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo <sup>a</sup> Based on number of subjects randomized <sup>b</sup> 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 <sup>c</sup> N = number of patients whose baseline Worst Pruritus NRS is ≥ 4 <sup>d</sup> N = number of patients whose baseline Worst Pruritus NRS is > 1 <sup>e</sup> % change = least squares mean percent change relative to baseline <sup>f</sup> multiplicity-controlled p < 0.001 upadacitinib + TCS vs placebo + TCS comparison <sup>g</sup> nominal p <0.001 upadacitinib + TCS vs placebo + TCS comparison			

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

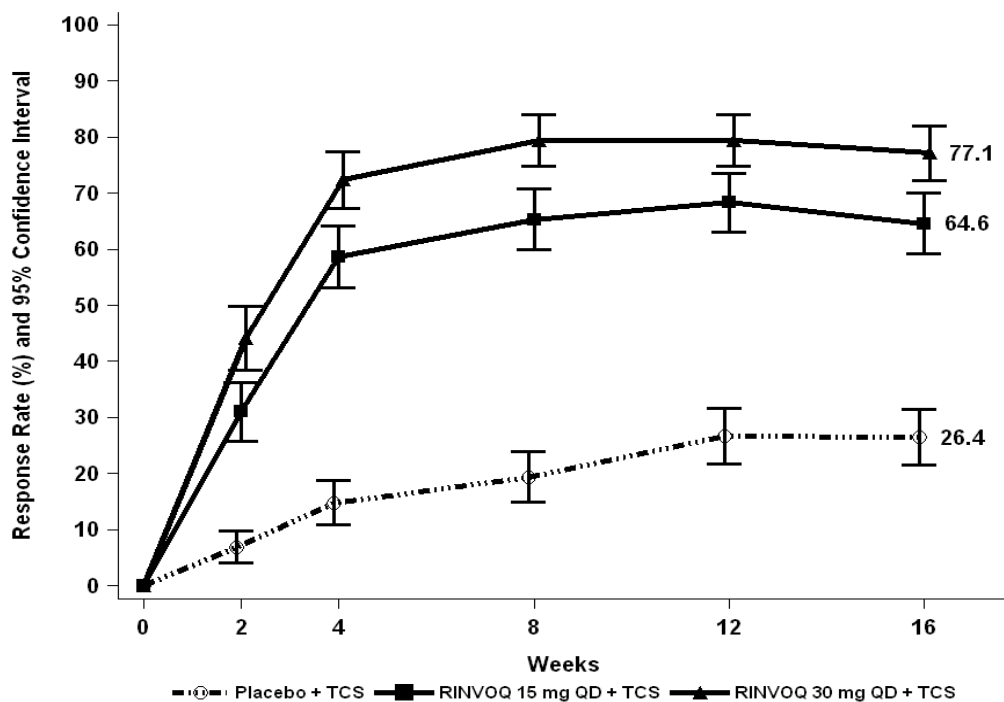
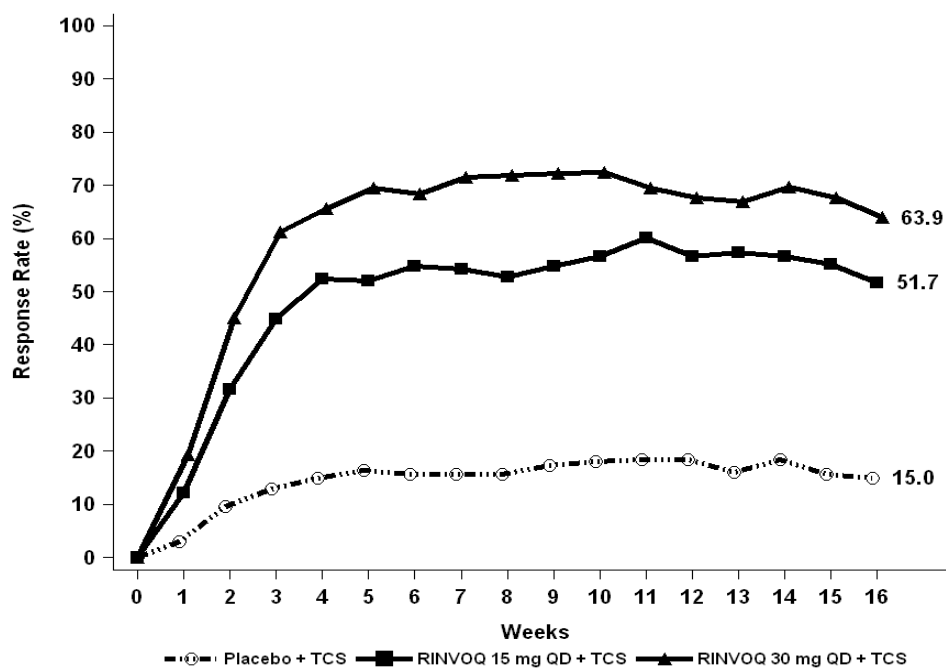


Figure 8: Proportion of patients with  $\geq 4$ -point improvement in the Worst Pruritus NRS in AD UP Study



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 13). 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  $\geq 8$  (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 13).

**Table 13. Patient reported outcomes results of RINVOQ monotherapy studies at week 16**

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

Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo  
The threshold values specified correspond to the minimal clinically important difference (MCID) and was used to determine response.

<sup>a</sup> N = number of patients whose baseline score is greater than or equal to the MCID.

<sup>b</sup> 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.

<sup>c</sup> ADerm-IS Sleep assesses difficulty falling asleep, sleep impact, and waking up at night due to AD.

<sup>d</sup> ADerm-IS Daily Activities assesses AD's effect on household activities, physical activities, social activities, and concentration.

<sup>e</sup> ADerm-IS Emotional State assesses self-consciousness, embarrassment, and sadness due to AD.

<sup>f</sup> N = number of patients whose baseline DLQI score is > 1.

<sup>g</sup> N = number of patients whose baseline HADS-A or HADS-D is ≥ 8.

<sup>h</sup> 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 14). The adverse event profile in adolescents was generally similar to that in adults. Safety and efficacy of RINVOQ in adolescents weighing less than 40 kg and in patients less than 12 years of age with atopic dermatitis have not been established.

**Table 14. Efficacy results of RINVOQ for adolescents at week 16**

Study Treatment Group	MEASURE UP 1		MEASURE UP 2		AD UP	
	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
<b>% responders</b>						
vIGA-AD 0/1 <sup>a,b</sup>	7.5%	38.1%	2.8%	42.4%	7.5%	30.8%
EASI 75 <sup>a</sup>	8.3%	71.4%	13.9%	66.7%	30.0%	56.4%
Worst Pruritus NRS <sup>c</sup> (≥ 4-point improvement)	15.4% N=39	45.0% N=40	2.8% N=36	33.3% N=30	13.2% N=38	41.7% N=36
Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo <sup>a</sup> Based on number of subjects randomized <sup>b</sup> 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 <sup>c</sup> N = number of patients whose baseline Worst Pruritus NRS is ≥ 4						

### Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in two Phase 3 randomised, double-blind, multicentre, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis (Table 15). All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. The studies include long-term extensions for up to 5 years (SELECT-PsA 1) and 3 years (SELECT-PsA 2).

**Table 15. Clinical Trial Summary**

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-PsA 1	Non-biologic DMARD-IR <sup>a</sup> (1705)	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• Placebo</li> <li>• Adalimumab 40 mg</li> </ul>	Primary Endpoint: <ul style="list-style-type: none"> <li>• ACR20 at Week 12</li> </ul> Key Secondary Endpoints: <ul style="list-style-type: none"> <li>• MDA at Week 24</li> <li>• Resolution of enthesitis (LEI=0) and dactylitis (LDI=0) at Week 24</li> <li>• PASI75 at Week 16</li> <li>• sIGA at Week 16</li> <li>• SAPS at Week 16</li> <li>• Radiographic progression (<math>\Delta</math>mTSS) at Week 24</li> <li>• <math>\Delta</math> Physical Function (HAQ-DI) at Week 12</li> <li>• SF-36 PCS at Week 12</li> <li>• FACIT-F at Week 12</li> <li>• ACR20, pain, and <math>\Delta</math> Physical Function (HAQ-DI) vs adalimumab at Week 12</li> </ul>
SELECT-PsA 2	bDMARD-IR <sup>b</sup> (642)	<ul style="list-style-type: none"> <li>• Upadacitinib 15 mg</li> <li>• Upadacitinib 30 mg</li> <li>• Placebo</li> </ul>	Primary Endpoint: <ul style="list-style-type: none"> <li>• ACR20 at Week 12</li> </ul> Key Secondary Endpoints: <ul style="list-style-type: none"> <li>• MDA at Week 24</li> <li>• PASI75 at Week 16</li> <li>• sIGA at Week 16</li> <li>• SAPS at Week 16</li> <li>• <math>\Delta</math> Physical Function (HAQ-DI) at Week 12</li> <li>• SF-36 PCS at Week 12</li> <li>• FACIT-F at Week 12</li> </ul>
<b>Abbreviations:</b> ACR20 = American College of Rheumatology $\geq$ 20% improvement bDMARD = biologic disease-modifying anti-rheumatic drug FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue score HAQ-DI = Health Assessment Questionnaire-Disability Index IR = inadequate responder MDA = minimal disease activity mTSS = modified Total Sharp Score PASI = Psoriasis Area and Severity Index SAPS = Self-Assessment of Psoriasis Symptoms SF-36 PCS = Short Form (36) Health Survey (SF-36) Physical Component Summary sIGA = static Investigator Global Assessment of psoriasis <sup>a</sup> Patients who had an inadequate response or intolerance to at least one non-biologic DMARD <sup>b</sup> Patients who had an inadequate response or intolerance to at least one bDMARD			

**Clinical Response**

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved ACR20 response compared to placebo at Week 12 (Table 16, Figure 9). In SELECT-PsA 1, RINVOQ 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at Week 12. A higher proportion of patients treated with RINVOQ 15 mg achieved

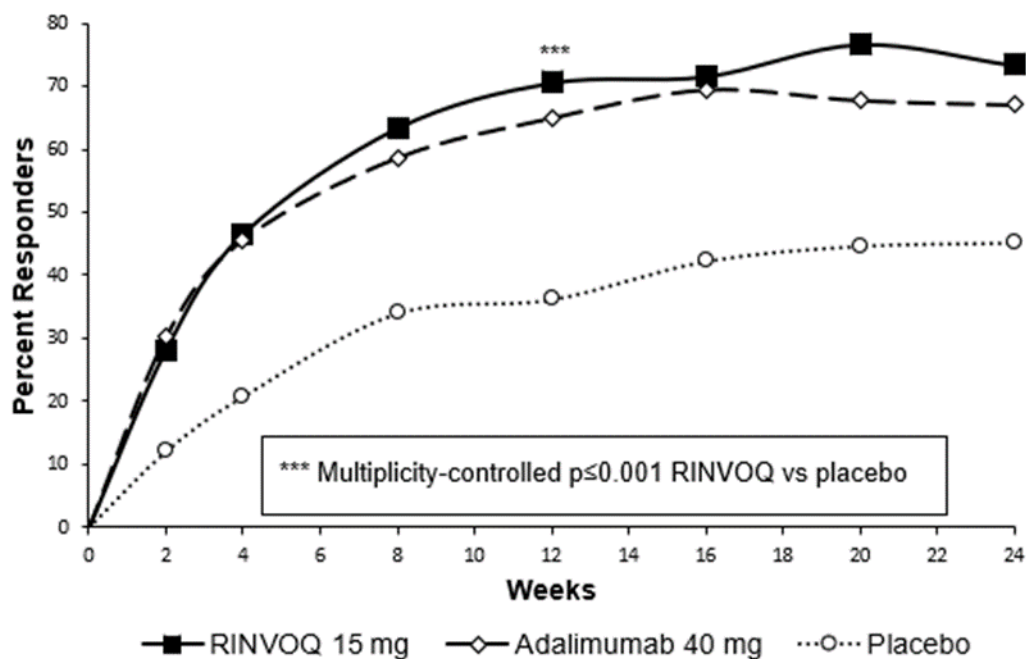
ACR50 and ACR70 responses at Week 12 compared to placebo. Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 2 for ACR20.

Treatment with RINVOQ 15 mg resulted in improvements in individual ACR components, including tender/painful and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP compared to placebo (Table 17). Treatment with RINVOQ 15 mg resulted in greater improvement in pain compared to adalimumab at Week 24.

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

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

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



**Table 16. Clinical Response**

Study	SELECT-PsA 1 non-biologic DMARD-IR			SELECT-PsA 2 bDMARD-IR	
	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
<b>ACR20 (% of patients)</b>					
Week 12	36	71 <sup>e</sup>	65	24	57 <sup>e</sup>
Week 24	45	73 <sup>f,i</sup>	67	20	59 <sup>f</sup>
Week 56		74	69		60
<b>ACR50 (% of patients)</b>					
Week 12	13	38 <sup>f</sup>	38	5	32 <sup>f</sup>
Week 24	19	52 <sup>f,i</sup>	44	9	38 <sup>f</sup>
Week 56		60 <sup>i</sup>	51		41
<b>ACR70 (% of patients)</b>					
Week 12	2	16 <sup>f</sup>	14	1	9 <sup>f</sup>
Week 24	5	29 <sup>f,i</sup>	23	1	19 <sup>f</sup>
Week 56		41 <sup>h</sup>	31		24
<b>MDA (% of patients)</b>					
Week 12	6	25 <sup>f</sup>	25	4	17 <sup>f</sup>
Week 24	12	37 <sup>e</sup>	33	3	25 <sup>e</sup>
Week 56		45	40		29
<b>Resolution of enthesitis (LEI=0; % of patients)<sup>a</sup></b>					
Week 12	33	47 <sup>f</sup>	47	20	39 <sup>f</sup>
Week 24	32	54 <sup>e</sup>	47	15	43 <sup>f</sup>
Week 56		59	54		43
<b>Resolution of dactylitis (LDI=0; % of patients)<sup>b</sup></b>					
Week 12	42	74 <sup>f</sup>	72	36	64 <sup>g</sup>
Week 24	40	77 <sup>f</sup>	74	28	58 <sup>g</sup>
Week 56		75	74		51
<b>PASI75 (% of patients)<sup>c</sup></b>					
Week 16	21	63 <sup>e</sup>	53	16	52 <sup>e</sup>
Week 24	27	64 <sup>f</sup>	59	19	54 <sup>f</sup>
Week 56		65	61		52
<b>PASI90 (% of patients)<sup>c</sup></b>					
Week 16	12	38 <sup>f</sup>	39	8	35 <sup>f</sup>
Week 24	17	42 <sup>f</sup>	45	7	36 <sup>f</sup>
Week 56		49	47		41
<b>PASI100 (% of patients)<sup>c</sup></b>					
Week 16	7	24 <sup>f</sup>	20	6	25 <sup>f</sup>
Week 24	10	27 <sup>f</sup>	28	5	22 <sup>f</sup>
Week 56		35	31		27
<b>sIGA 0/1 (% of patients)<sup>d</sup></b>					
Week 16	11	42 <sup>e</sup>	39	9	37 <sup>e</sup>



Week 24	12	45 <sup>f</sup>	41	10	33 <sup>f</sup>
Week 56		52	47		33

**Abbreviations:**

ACR20 (or 50 or 70) = American College of Rheumatology  $\geq 20\%$  (or  $\geq 50\%$  or  $\geq 70\%$ ) improvement

ADA = adalimumab

bDMARD = biologic disease-modifying anti-rheumatic drug

IR = inadequate responder

MDA = minimal disease activity

PASI75 (or 90 or 100) =  $\geq 75\%$  (or  $\geq 90\%$  or 100%) improvement in Psoriasis Area and Severity Index

PBO = placebo

sIGA = static Physician Global Assessment

UPA= upadacitinib

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.

<sup>a</sup>. 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)

<sup>b</sup>. 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)

<sup>c</sup>. In patients with  $\geq 3\%$  BSA psoriasis at baseline (n=211, 214, and 211, respectively, for SELECT-PsA 1 and n=131 and 130, respectively, for SELECT-PsA 2)

<sup>d</sup>. In patients with sIGA  $\geq 2$  at baseline (n=313, 322, and 330, respectively, for SELECT-PsA 1 and n=163 and 171, respectively, for SELECT-PsA 2)

<sup>e</sup>. multiplicity-controlled  $p \leq 0.001$  upadacitinib vs placebo comparison

<sup>f</sup>. nominal  $p \leq 0.001$  upadacitinib vs placebo comparison

<sup>g</sup>. nominal  $p \leq 0.01$  upadacitinib vs placebo comparison

<sup>h</sup>. nominal  $p \leq 0.01$  upadacitinib vs adalimumab comparison

<sup>i</sup>. nominal  $p < 0.05$  upadacitinib vs adalimumab comparison

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

Study	SELECT-PsA 1 non-biologic DMARD-IR			SELECT-PsA 2 bDMARD-IR	
	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
<b>Number of tender/painful joints (0-68)</b>					
Week 12	-7.1	-11.3 <sup>d</sup>	-10.3	-6.2	-12.4 <sup>d</sup>
Week 24	-9.2	-13.7 <sup>d</sup>	-12.5	-6.6	-14.0 <sup>d</sup>
Week 56		-16.2	-15.8		-18.0
<b>Number of swollen joints (0-66)</b>					
Week 12	-5.3	-7.9 <sup>d</sup>	-7.6	-4.8	-7.1 <sup>d</sup>
Week 24	-6.3	-9.0 <sup>d</sup>	-8.6	-5.6	-8.3 <sup>d</sup>
Week 56		-10.1	-10.2		-9.4
<b>Patient assessment of pain<sup>a</sup></b>					
Week 12	-0.9	-2.3 <sup>d</sup>	-2.3	-0.5	-1.9 <sup>d</sup>
Week 24	-1.4	-3.0 <sup>d, f</sup>	-2.6	-0.7	-2.2 <sup>d</sup>
Week 56		-3.5 <sup>g</sup>	-3.0		-2.8
<b>Patient global assessment<sup>a</sup></b>					
Week 12	-1.2	-2.7 <sup>d</sup>	-2.6	-0.6	-2.3 <sup>d</sup>
Week 24	-1.6	-3.4 <sup>d, e</sup>	-2.9	-0.8	-2.6 <sup>d</sup>
Week 56		-3.8 <sup>f</sup>	-3.2		-3.1
<b>Disability index (HAQ-DI)<sup>b</sup></b>					
Week 12	-0.14	-0.42 <sup>c, g</sup>	-0.34	-0.10	-0.30 <sup>c</sup>
Week 24	-0.19	-0.51 <sup>d, e</sup>	-0.39	-0.08	-0.33 <sup>d</sup>
Week 56		-0.56 <sup>f</sup>	-0.44		-0.38
<b>Physician global assessment<sup>a</sup></b>					
Week 12	-2.1	-3.6 <sup>d</sup>	-3.4	-1.4	-3.1 <sup>d</sup>
Week 24	-2.8	-4.3 <sup>d</sup>	-4.1	-1.8	-3.8 <sup>d</sup>
Week 56		-5.0	-4.8		-4.7
<b>hsCRP (mg/L)</b>					
Week 12	-1.3	-7.1 <sup>d</sup>	-7.6	0.3	-6.6 <sup>d</sup>
Week 24	-2.1	-7.6 <sup>d</sup>	-7.3	-0.9	-6.3 <sup>d</sup>
Week 56		-7.8	-7.2		-6.5
<b>Abbreviations:</b> ACR = American College of Rheumatology ADA = adalimumab hsCRP = high sensitivity C-reactive protein HAQ-DI = Health Assessment Questionnaire-Disability Index IR = inadequate responder PBO = placebo UPA = upadacitinib <sup>a</sup> . Numeric rating scale (NRS): 0 = best, 10 = worst <sup>b</sup> . Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8					

categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.  
c. multiplicity-controlled  $p \leq 0.001$  upadacitinib vs placebo comparison  
d. nominal  $p \leq 0.001$  upadacitinib vs placebo comparison  
e. nominal  $p \leq 0.001$  upadacitinib vs adalimumab comparison  
f. nominal  $p \leq 0.01$  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 18). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change  $\leq 0.5$ ) was higher with RINVOQ 15 mg compared to placebo at Week 24.

**Table 18. Radiographic Changes in SELECT-PsA-1**

Treatment Group	PBO	UPA 15 mg	ADA 40 mg
<b>Modified Total Sharp Score, mean change from baseline</b>			
Week 24	0.25	-0.04 <sup>c</sup>	0.01
Week 56 <sup>a</sup>	0.44	-0.05 <sup>d</sup>	-0.06
<b>Erosion Score, mean change from baseline</b>			
Week 24	0.12	-0.03 <sup>d</sup>	0.01
Week 56 <sup>a</sup>	0.30	-0.03 <sup>d</sup>	-0.05
<b>Joint Space Narrowing Score, mean change from baseline</b>			
Week 24	0.10	-0.00 <sup>f</sup>	-0.02
Week 56 <sup>a</sup>	0.14	-0.03 <sup>e</sup>	-0.03
<b>Proportion of patients with no radiographic progression<sup>b</sup></b>			
Week 24	92	96 <sup>f</sup>	95
Week 56 <sup>a</sup>	89	97 <sup>d</sup>	94
<b>Abbreviations:</b>			
ADA = adalimumab; PBO = placebo; UPA= upadacitinib			
<sup>a</sup> All placebo data at Week 56 derived using linear extrapolation			
<sup>b</sup> No progression defined as mTSS change ≤0.5			
<sup>c</sup> multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison			
<sup>d</sup> nominal p≤0.001 upadacitinib vs placebo comparison			
<sup>e</sup> nominal p≤0.01 upadacitinib vs placebo comparison			
<sup>f</sup> nominal p<0.05 upadacitinib vs placebo comparison			

### Physical Function Response and Health-Related Outcomes

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

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

Health-related quality of life was assessed by SF-36. In both studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared to placebo at Week 12. Greater improvement was also observed compared to adalimumab. Greater improvement was observed in the Mental Component Summary score and all 8 domains of SF-36 (Physical Functioning, Bodily Pain, Vitality, Social Functioning,

Role Physical, General Health, Role Emotional, and Mental Health) compared to placebo. Improvements from baseline were maintained through Week 56 in both studies.

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

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

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

#### Ankylosing Spondylitis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in a randomised, double-blind, multicentre, placebo-controlled study in patients 18 years of age or older with active ankylosing spondylitis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)  $\geq 4$  and Patient's Assessment of Total Back Pain score  $\geq 4$  (Table 19). The study included a long-term extension for up to 2 years.

**Table 19. Clinical Trial Summary**

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-AXIS 1	NSAID-IR <sup>a,b</sup> bDMARD-naïve (187)	<ul style="list-style-type: none"> <li>Upadacitinib 15 mg</li> <li>Placebo</li> </ul>	Primary Endpoint: <ul style="list-style-type: none"> <li>ASAS40 at Week 14</li> </ul>
			Key Secondary Endpoints at Week 14: <ul style="list-style-type: none"> <li>ASAS Partial Remission</li> <li>BASDAI 50</li> <li>ASDAS-CRP</li> <li>BASFI</li> <li>SPARCC MRI score (spine)</li> </ul>
<p><b>Abbreviations:</b>            ASAS40 = Assessment of SpondyloArthritis international Society ≥40% improvement            ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein            BASDAI = Bath Ankylosing Spondylitis Disease Activity Index            BASFI = Bath Ankylosing Spondylitis Functional Index            bDMARD = biologic disease-modifying anti-rheumatic drug            IR = inadequate responder            NSAID = Nonsteroidal Anti-inflammatory Drug            SPARCC MRI = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging  <sup>a</sup>Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindication for NSAIDs  <sup>b</sup>At baseline, approximately 16% of the patients were on a concomitant csDMARD.</p>			

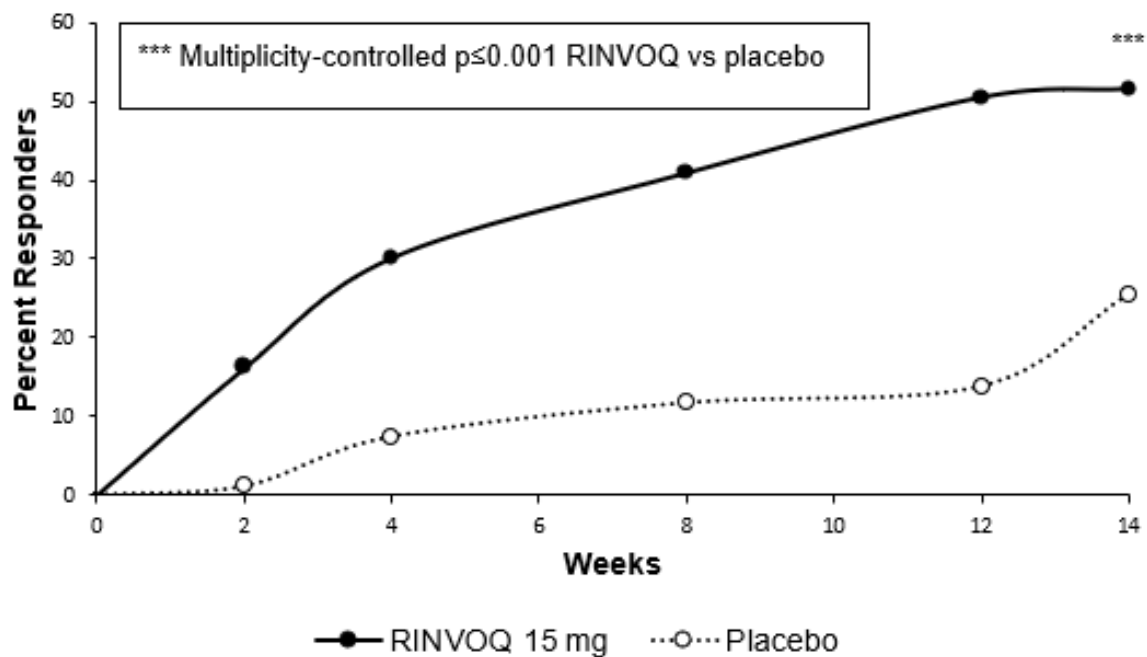
**Clinical Response**

In SELECT-AXIS 1, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 20, Figure 10). Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 2 for ASAS40 which was maintained through Week 64.

Treatment with RINVOQ 15 mg resulted in improvements in individual ASAS components, including patient global assessment of disease activity, total back pain assessment, inflammation, and function compared to placebo (Table 21).

The efficacy of RINVOQ 15 mg was demonstrated regardless of subgroups evaluated including gender, baseline BMI, symptom duration of AS, and baseline hsCRP.

Figure 10. Percent of Patients Achieving ASAS40



**Table 20. Clinical Response in SELECT-AXIS-1**

Treatment Group	PBO	UPA 15 mg
N	94	93
<b>ASAS40 (% of patients)</b>		
Week 14	25.5	51.6 <sup>a</sup>
Week 52		80.2
<b>ASAS20 (% of patients)</b>		
Week 14	40.4	64.5 <sup>c</sup>
Week 52		87.7
<b>ASAS Partial Remission (% of patients)</b>		
Week 14	1.1	19.4 <sup>a</sup>
Week 52		50.0
<b>BASDAI 50 (% of patients)</b>		
Week 14	23.4	45.2 <sup>b</sup>
Week 52		77.8
<b>Change from baseline in ASDAS-CRP</b>		
Week 14	-0.54	-1.45 <sup>a</sup>
Week 52		-2.05
<b>ASDAS Inactive Disease (% of patients)</b>		
Week 14	0	16.1 <sup>c</sup>
Week 52		46.2
<b>ASDAS Low Disease Activity (% of patients)<sup>d</sup></b>		
Week 14	10.6	49.5 <sup>c</sup>
Week 52		85.9
<b>ASDAS Major Improvement (% of patients)</b>		
Week 14	5.3	32.3 <sup>c</sup>
Week 52		55.8
<p><b>Abbreviations:</b>  ASAS20 (or 40) = Assessment of SpondyloArthritis international Society ≥20% (or ≥40%) improvement  ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein  BASDAI = Bath Ankylosing Spondylitis Disease Activity Index  PBO = placebo  UPA= upadacitinib  <sup>a</sup>.multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison  <sup>b</sup>.multiplicity-controlled p≤0.01 upadacitinib vs placebo comparison  <sup>c</sup>.nominal p≤0.001 upadacitinib vs placebo comparison  <sup>d</sup>. post-hoc analysis  For binary endpoints, Week 14 results are based on non-responder imputation analysis.  For continuous endpoints, Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measure analysis. For binary and continuous endpoints, Week 52 results are based on as-observed data.</p>		



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

Treatment Group	PBO	UPA 15 mg
N	94	93
<b>Patient Global Assessment of Disease Activity<sup>a</sup></b>		
Week 14	-1.31	-2.96 <sup>e</sup>
Week 52		-4.54
<b>Total Back Pain<sup>a</sup></b>		
Week 14	-1.68	-3.21 <sup>e</sup>
Week 52		-4.75
<b>BASFI<sup>b</sup></b>		
Week 14	-1.30	-2.29 <sup>d</sup>
Week 52		-3.71
<b>Inflammation<sup>c</sup> (0-10)</b>		
Week 14	-1.90	-3.15 <sup>e</sup>
Week 52		-4.80
<b>Abbreviations:</b> ASAS = Assessment of SpondyloArthritis international Society BASFI = Bath Ankylosing Spondylitis Functional Index PBO = placebo UPA= upadacitinib Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis; Week 52 results are based on as-observed data. <sup>a</sup> Numeric rating scale (NRS): 0 = best, 10 = worst <sup>b</sup> BASFI: 0 = best, 10 = worst <sup>c</sup> mean of BASDAI questions 5 and 6 assessing morning stiffness severity and duration: 0 = best, 10 = worst <sup>d</sup> multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison <sup>e</sup> nominal p≤0.001 upadacitinib vs placebo comparison		

### Physical Function and Health-Related Outcomes

Patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by the BASFI at Week 14 (Table 21). These improvements were maintained through Week 64.

Patients treated with RINVOQ 15 mg showed greater improvement in back pain as assessed by the Total Back Pain component of ASAS response compared to placebo at Week 14. 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) and nocturnal back pain. Improvements in total and nocturnal back pain were observed as early as Week 2. Pain improvements were maintained through Week 64.

## 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. 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.

At Week 14, patients treated with RINVOQ 15 mg demonstrated greater improvement of inflammatory signs as measured by hsCRP compared to placebo. Decrease in hsCRP was maintained through Week 64.

## 5.2 Pharmacokinetic properties

Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once-daily administrations. The pharmacokinetic properties of RINVOQ are provided in Table 22.

**Table 22. Pharmacokinetic Properties of RINVOQ**

<b>Absorption</b>	
T <sub>max</sub> (h)	2-4
Effect of high-fat meal (relative to fasting)	No clinically relevant effect AUC: ↑ 29%, C <sub>max</sub> ↑ 39%
<b>Distribution</b>	
% Bound to human plasma proteins	52
Blood-to-plasma ratio	1.0
<b>Metabolism</b>	
Metabolism	CYP3A4, CYP2D6 (minor) No active metabolites
<b>Elimination</b>	
Terminal phase elimination t <sub>1/2</sub> (h)	9-14
% of dose excreted unchanged in urine <sup>a</sup>	24
% of dose excreted unchanged in faeces <sup>a</sup>	38
% of dose excreted as metabolites <sup>a</sup>	34
<sup>a</sup> Based on single dose administration of [ <sup>14</sup> C] upadacitinib immediate-release solution in a mass balance study.	

## Pharmacokinetics in special populations

### **Renal Impairment**

Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib  $C_{max}$  was similar in subjects with normal and impaired renal function. Mild or moderate renal impairment has no clinically relevant effect on upadacitinib exposure for the 15 or 30 mg once daily dosing regimens. The recommended dose is 15 mg once daily for patients with severe renal impairment.

### **Hepatic Impairment**

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib  $C_{max}$  was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C).

### **Other Intrinsic Factors**

Age, sex, body weight, race, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure. Upadacitinib pharmacokinetics are consistent between rheumatoid arthritis, atopic dermatitis, psoriatic arthritis and ankylosing spondylitis patients.

## 5.3 Pre-clinical safety data

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

### **Genotoxicity**

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

### **Carcinogenicity**

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of Excipients**

Each tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, silica (colloidal anhydrous), and magnesium stearate.

Film coating contains polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), iron oxide black (E172) and iron oxide red (E172).

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

RINVOQ 15 mg modified release tablets: 24 months

### **6.4 Special precautions for storage**

Store below 30°C.

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

### **6.5 Nature and contents of container**

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

The following presentations are available:

Starter Pack 15 mg (7 tablets) - 1 carton containing one blister with 7 tablets.

Monthly Pack 15 mg (28 tablets) - 1 carton containing four blisters with 7 tablets in each blister. Not all presentations may be marketed.

### **6.6 Special precautions for disposal**

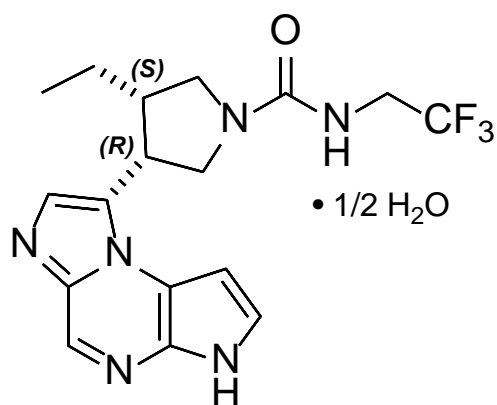
Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 Physicochemical properties

Upadacitinib is a white to light brown powder with the following chemical name: (3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1).

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

Upadacitinib has a molecular weight of 389.38 g/mol and a molecular formula of  $C_{17}H_{19}F_3N_6O \cdot \frac{1}{2} H_2O$ . The chemical structure of upadacitinib is:



### CAS number

1310726-60-3

## 7 MEDICINE SCHEDULE

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## 9 DATE OF FIRST APPROVAL

19 November 2020

## 10 DATE OF REVISION

4 November 2021

Summary table of changes

<b>Section Changed</b>	<b>Summary of new information</b>
4.1 Therapeutic indications	Inclusion of Psoriatic arthritis (PsA) and Ankylosing Spondylitis (AS) indications.
4.2 Dose and Method of Administration	Inclusion of dosing for PsA and AS.
4.4 Special warnings and precautions for use	Updated information for Use in the Elderly
4.8 Adverse Effects (Undesirable effects)	Editorial changes and updated information for PsA and AS
5.0 Pharmacological properties	Updated Clinical Trial data for PsA and AS
5.2 Pharmacokinetic Properties	Update to Other intrinsic Factors