RINVOQ®

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
RINVOQ 30 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ 15 mg prolonged-release tablets

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

RINVOQ 30 mg prolonged-release tablets

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

RINVOQ 15 mg prolonged-release tablets

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

RINVOQ 30 mg prolonged-release tablets

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

4. CLINICAL PARTICULARS

Patient safety information Card
The marketing of RINVOQ is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

HCP educational brochure
This product is marketed with HCP educational brochure providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

4.1 Therapeutic indications

Rheumatoid arthritis

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

anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.

Psoriatic arthritis

RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate.

Ankylosing spondylitis

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

Atopic dermatitis

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

4.2 Posology and method of administration

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

Posology

Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
The recommended dose of upadacitinib is 15 mg once daily.

Consideration should be given to discontinuing treatment in patients with ankylosing spondylitis who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Atopic dermatitis

Adults
The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation.

- A dose of 30 mg once daily may be appropriate for patients with high disease burden.
- A dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily.
- The lowest effective dose for maintenance should be considered.

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

Adolescents (from 12 to 17 years of age)
The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.

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

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

Dose initiation

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

Dose interruption

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

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

Table 1. Laboratory measures and monitoring guidance

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

Special populations

Elderly

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

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

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment (see section 5.2). Upadacitinib 15 mg once daily was not evaluated in clinical trials in patients with eGFR<40 mL/min/1.73 m^2. Upadacitinib should be used with caution in patients with severe renal impairment. Upadacitinib 30 mg once daily is not recommended for patients with severe renal impairment. The use of upadacitinib has not been studied in subjects with end stage renal disease.

Hepatic impairment

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

Paediatric population

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

The safety and efficacy of RINVOQ in children and adolescents with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis aged 0 to less than 18 years have not yet been established. No data are available.

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Immunosuppressive medicinal products

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

Serious infections

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

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

Consider the risks and benefits of treatment prior to initiating upadacitinib in patients:

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

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

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

Tuberculosis

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

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

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

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was reported in clinical studies (see section 4.8). The risk of herpes zoster appears to be higher in Japanese patients treated with upadacitinib. If a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with upadacitinib. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies. If hepatitis B virus DNA is detected while receiving upadacitinib, a liver specialist should be consulted.

Vaccination

No data are available on the response to vaccination with live vaccines in patients receiving upadacitinib. Use of live, attenuated vaccines during or immediately prior to upadacitinib therapy is not recommended. Prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines. (see section 5.1 for data on inactivated pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) and concomitant use with upadacitinib).

Malignancy

The risk of malignancies, including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medicinal products may increase the risk of malignancies, including lymphoma. The clinical data are currently limited and long-term studies are ongoing.

Malignancies were observed in clinical studies of upadacitinib. The risks and benefits of upadacitinib treatment should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing upadacitinib therapy in patients who develop a malignancy.

Non-melanoma skin cancer

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

Haematological abnormalities

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

Diverticulitis

Events of diverticulitis have been reported in clinical trials and from post-marketing sources. Diverticulitis may cause gastrointestinal perforation. Upadacitinib should be used with caution in patients with diverticular disease and especially in patients chronically treated with concomitant medications associated with an increased risk of diverticulitis: nonsteroidal anti-inflammatory drugs, corticosteroids, and opioids. Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis to prevent gastrointestinal perforation

Cardiovascular risk

Rheumatoid arthritis patients have an increased risk for cardiovascular disorders. Patients treated with upadacitinib should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

Lipids

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

Hepatic transaminase elevations

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

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

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

Venous thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including upadacitinib. Upadacitinib should be used with caution in patients at high risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, patients undergoing major surgery, and prolonged immobilisation. If clinical features of DVT/PE occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect the pharmacokinetics of upadacitinib

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

Coadministration with CYP3A4 inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin). In a clinical study, coadministration of upadacitinib with ketoconazole resulted in 70% and 75% increases in upadacitinib C_{max} and AUC, respectively. Upadacitinib 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. Upadacitinib 30 mg once daily dose is not recommended for patients receiving chronic treatment with strong CYP3A4 inhibitors. Alternatives to strong CYP3A4 inhibitor medications should be considered when used in the long-term.

Coadministration with CYP3A4 inducers

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

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

Potential for upadacitinib to affect the pharmacokinetics of other medicinal products

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Upadacitinib is contraindicated during pregnancy (see section 4.3).

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

Breast-feeding

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

A risk to newborns/infants cannot be excluded.

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In the placebo-controlled clinical trials for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, the most commonly reported adverse reactions (≥2% of patients in at least one of the indications with the highest rate among indications presented) with upadacitinib 15 mg were upper respiratory tract infections (19.5%), blood creatine phosphokinase (CPK) increased (8.6%), alanine transaminase increased (4.3%), bronchitis (3.9%), nausea (3.5%), cough (2.2%), aspartate transaminase increased (2.2%), and hypercholesterolaemia (2.2%).

In the placebo-controlled atopic dermatitis clinical trials, the most commonly reported adverse reactions (≥2% of patients) with upadacitinib 15 mg or 30 mg were upper respiratory tract infection (25.4%), acne (15.1%), herpes simplex (8.4%), headache (6.3%), CPK increased (5.5%), cough

(3.2%), folliculitis (3.2%), abdominal pain (2.9%), nausea (2.7%), neutropenia (2.3%), pyrexia (2.1%), and influenza (2.1%).

The most common serious adverse reactions were serious infections (see section 4.4).

The safety profile of upadacitinib with long-term treatment was generally similar to the safety profile during the placebo-controlled period across indications.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical studies.
The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). The frequencies in Table 2 are based on the higher of the rates for adverse reactions reported with RINVOQ 15 mg in rheumatologic disease and atopic dermatitis clinical trials, or RINVOQ 30 mg in atopic dermatitis clinical trials. When notable differences in frequency were observed between indications, these are presented in the footnotes below the table.

Table 2. Adverse reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)[a]	Bronchitis [a,b] Herpes zoster Herpes simplex[a] Folliculitis Influenza Urinary tract infection	Pneumonia Oral candidiasis Diverticulitis
Blood and lymphatic system disorders		Anaemia Neutropaenia	
Metabolism and nutrition disorders		Hypercholesterolaemia[b]	Hypertriglyceridaemia
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Abdominal pain[a] Nausea	
Skin and subcutaneous tissue disorders	Acne[c]	Urticaria[c]	
General disorders and administration site conditions		Fatigue Pyrexia	
Investigations		Blood CPK increased ALT increased[b] AST increased[b] Weight increased	
Nervous system disorders		Headache	

[a] Presented as grouped term
[b] In atopic dermatitis trials, the frequency of bronchitis, hypercholesterolaemia, ALT increased, and AST increased was uncommon.
[c] In rheumatologic disease trials, the frequency was common for acne and uncommon for urticaria

Description of selected adverse reactions

Rheumatoid arthritis

Infections

In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the upadacitinib 15 mg group was 27.4% compared to 20.9% in the placebo group. In methotrexate (MTX)-controlled studies, the frequency of infection over 12/14 weeks in the upadacitinib 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group. The overall long-term rate of infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies (2,630 patients) was 93.7 events per 100 patient-years.

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

Opportunistic infections (excluding tuberculosis)

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

The long-term rate of herpes zoster for the upadacitinib 15 mg group across all five Phase 3 clinical studies was 3.7 events per 100 patient-years. Most of the herpes zoster events involved a single dermatome and were non-serious.

Hepatic transaminase elevations

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

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

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

Lipid elevations

Upadacitinib 15 mg treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol. There was no change in the LDL/HDL ratio. Elevations were observed at 2 to 4 weeks of treatment and remained stable with longer-term treatment. Among patients in the controlled studies with baseline values below the

specified limits, the following frequencies of patients were observed to shift to above the specified limits on at least one occasion during 12/14 weeks (including patients who had an isolated elevated value):

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

Creatine phosphokinase

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

Neutropaenia

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

Psoriatic arthritis

Overall, the safety profile observed in patients with active psoriatic arthritis treated with upadacitinib 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher rate of serious infections (2.6 events per 100 patient-years and 1.3 events per 100 patient-years, respectively) and hepatic transaminase elevations (ALT elevations Grade 3 and higher rates 1.4% and 0.4%, respectively) was observed in patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy.

Ankylosing spondylitis

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

Atopic dermatitis

Infections

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

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

Opportunistic infections (excluding tuberculosis)

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

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

Laboratory abnormalities

Dose-dependent changes in ALT increased and/or AST increased (≥ 3 x ULN), lipid parameters, CPK values (> 5 x ULN), and neutropenia *(*ANC < 1 x 10^9 cells/L) associated with upadacitinib treatment were similar to what was observed in the rheumatologic disease clinical studies.

Small increases in LDL cholesterol were observed after week 16 in atopic dermatitis studies.

Elderly

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

Paediatric population

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants ATC code: L04AA44

Mechanism of action

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

In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Atopic dermatitis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus.

Pharmacodynamic effects

Inhibition of IL-6 induced STAT3 and IL-7 induced STAT5 phosphorylation

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

Lymphocytes

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

hsCRP

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

Vaccine study

The influence of upadacitinib on the humoral response following the administration of inactivated pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) 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. The primary endpoint was the proportion of patients with satisfactory humoral response defined as ≥ 2-fold increase in antibody concentration from baseline to Week 4 in at least 6 out of the 12 pneumococcal antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Results at Week 4 demonstrated a satisfactory humoral response in 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with upadacitinib 15 mg and 30 mg, respectively.

Clinical efficacy and safety

Rheumatoid arthritis

The efficacy and safety of upadacitinib 15 mg once daily was assessed in five Phase 3 randomised, double-blind, multicentre studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria (see Table 3). 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. All studies included long-term extensions for up to 5 years.

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

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

Table 3: Clinical trials summary

Study name	Population (n)	Treatment arms	Key outcome measures
SELECT-EARLY	MTX-naïve[a] (947)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	• Primary endpoint: clinical remission (DAS28-CRP) at week 24 • Low disease activity (DAS28-CRP) • ACR50 • Radiographic progression (mTSS) • Physical function (HAQ-DI) • SF-36 PCS
SELECT-MONOTHERAPY	MTX-IR[b] (648)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	• Primary endpoint: low disease activity (DAS28-CRP) at week 14 • Clinical remission (DAS28-CRP) • ACR20 • Physical function (HAQ-DI) • SF-36 PCS • Morning stiffness
SELECT-NEXT	csDMARD-IR[c] (661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• Primary endpoint: low disease activity (DAS28-CRP) at week 12 • Clinical remission (DAS28-CRP) • ACR20 • Physical function (HAQ-DI) • SF-36 PCS • Low disease activity (CDAI) • Morning stiffness • FACIT-F
SELECT-COMPARE	MTX-IR[d] (1,629)	• Upadacitinib 15 mg • Placebo • Adalimumab 40 mg On background MTX	• Primary endpoint: clinical remission (DAS28-CRP) at week 12 • Low disease activity (DAS28-CRP) • ACR20 • Low disease activity (DAS28-CRP) vs adalimumab • Radiographic progression (mTSS) • Physical function (HAQ-DI) • SF-36 PCS • Low disease activity (CDAI) • Morning stiffness

			• FACIT-F
SELECT-BEYOND	bDMARD-IR[e] (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• Primary endpoint: low disease activity (DAS28-CRP) at week 12 • ACR20 • Physical function (HAQ-DI) • SF-36 PCS

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

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

[b] Patients had inadequate response to MTX

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

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

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

Clinical response

Remission and low disease activity

In the studies, a significantly higher proportion of patients treated with upadacitinib 15 mg achieved low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX or adalimumab (Table 4). Compared to adalimumab, significantly higher rates of low disease activity were achieved at week 12 in SELECT-COMPARE. Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX.

ACR response

In all studies, more patients treated with upadacitinib 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo, MTX, or adalimumab (Table 4). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained for at least 1 year.

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

Table 4: 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											
LDA DAS28-CRP ≤3.2 (% of patients)											
12[a]/14[b]	28	53[g]	19	45[e]	17	48[e]	14	45[e,h]	29	14	43[e]
24[c]26[d]	32	60[f]					18	55[g,h]	39		
48	39	59[g]						50[h]	35		
CR DAS28-CRP <2.6 (% of patients)											
12[a]/14[b]	14	36[g]	8	28[e]	10	31[e]	6	29[e,h]	18	9	29[g]
24[c]26[d]	18	48[e]					9	41[g,h]	27		
48	29	49[g]						38[i]	28		
ACR20 (% of patients)											
12[a]/14[b]	54	76[g]	41	68[e]	36	64[e]	36	71[e,j]	63	28	65[e]
24[c]/26[d]	59	79[g]					36	67[g,i]	57		
48	57	74[g]						65[i]	54		
ACR50 (% of patients)											
12[a]/14[b]	28	52[g]	15	42[g]	15	38[g]	15	45[g,h]	29	12	34[g]
24[c]/26[d]	33	60[e]					21	54[g,h]	42		
48	43	63[g]						49[i]	40		
ACR70 (% of patients)											
12[a]/14[b]	14	32[g]	3	23[g]	6	21[g]	5	25[g,h]	13	7	12
24[c]/26[d]	18	44[g]					10	35[g,h]	23		
48	29	51[g]						36[h]	23		
CDAI ≤10 (% of patients)											
12[a]/14[b]	30	46[g]	25	35[l]	19	40[e]	16	40[e,h]	30	14	32[g]
24[c]/26[d]	38	56[g]					22	53[g,h]	38		
48	43	60[g]						47[h]	34		

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; ADA = adalimumab; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints; IR = inadequate responder; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; UPA= upadacitinib

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

[b] SELECT-MONOTHERAPY

[c] SELECT-EARLY

[d] SELECT-COMPARE

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

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

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

[h] nominal p≤0.001upadacitinib vs adalimumab comparison

[i] nominal p≤0.01 upadacitinib vs adalimumab comparison

[j] nominal p<0.05 upadacitinib vs adalimumab comparison

[k] nominal p≤0.01 upadacitinib vs placebo or MTX comparison

[l] nominal p<0.05 upadacitinib vs MTX comparison

Note: Week 48-data derived from analysis on Full Analysis set (FAS) by randomised group using Non-Responder Imputation

Radiographic response

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

Treatment with upadacitinib 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo in combination with MTX in SELECT-COMPARE and as monotherapy compared to MTX in SELECT-EARLY (Table 5). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with upadacitinib 15 mg in both studies.

Table 5: Radiographic changes

Study	**SELECT EARLY MTX-Naïve**		**SELECT COMPARE MTX-IR**		
Treatment Group	MTX	UPA 15 mg	PBO[a]	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline					
Week 24[b]/26[c]	0.7	0.1[f]	0.9	0.2[g]	0.1
Week 48	1.0	0.03[e]	1.7	0.3[e]	0.4
Proportion of patients with no radiographic progression[d]					
Week 24[b]/26[c]	77.7	87.5[f]	76.0	83.5[f]	86.8
Week 48	74.3	89.9[e]	74.1	86.4[e]	87.9

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

Physical function response and health-related outcomes

Treatment with upadacitinib 15 mg, alone or in combination with csDMARDs, resulted in a significantly greater improvement in physical function compared to all comparators as measured by HAQ-DI (see Table 6).

Table 6: Mean change from baseline in HAQ-DI[a,b]

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

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

[a] Data shown are mean

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

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

[d] SELECT-MONOTHERAPY

[e] SELECT-EARLY

[f] SELECT-COMPARE

[g] multiplicity-controlled $p \leq 0.001$ upadacitinib vs placebo or MTX comparison

[h] nominal $p \leq 0.001$ upadacitinib vs placebo or MTX comparison

[i] nominal $p \leq 0.01$ upadacitinib vs adalimumab comparison

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

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

Psoriatic arthritis

The efficacy and safety of upadacitinib 15 mg once daily were assessed in two Phase 3 randomised, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. For both studies, the primary endpoint was the proportion of patients who achieved an ACR20 response at week 12.

SELECT-PsA 1 was a 24-week trial in 1705 patients who had an inadequate response or intolerance to at least one non-biologic DMARD. At baseline, 1393 (82%) of patients were on at least one concomitant non-biologic DMARD; 1084 (64%) of patients received concomitant MTX only; and 311 (18%) of patients were on monotherapy. Patients received upadacitinib 15 mg or 30 mg once daily, adalimumab, or placebo. At week 24, all patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg once daily in a blinded manner. SELECT-PsA 1 included a long-term extension for up to 5 years.

SELECT-PsA 2 was a 24-week trial in 642 patients who had an inadequate response or intolerance to at least one biologic DMARD. At baseline, 296 (46%) of patients were on at least one concomitant non-biologic DMARD; 222 (35%) of patients received concomitant MTX only; and 345 (54%) of patients were on monotherapy. Patients received upadacitinib 15 mg or 30 mg once daily or placebo. At week 24, all patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg once daily in a blinded manner. SELECT-PsA 2 included a long-term extension for up to 3 years.

Clinical response

In both studies, a statistically significant greater proportion of patients treated with upadacitinib 15 mg achieved ACR20 response compared to placebo at week 12 (Table 7). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 2 for ACR20.

Treatment with upadacitinib 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.

In SELECT-PsA 1, upadacitinib 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at week 12; however, superiority to adalimumab could not be demonstrated.

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

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

Table 7: Clinical response in SELECT-PsA 1 and SELECT-PsA 2

Study	**SELECT-PsA 1 non-biologic DMARD-IR**			**SELECT-PsA 2 bDMARD-IR**	
Treatment Group	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
ACR20, % of patients (95% CI)					
Week 12	36 (32, 41)	71 (66, 75)[f]	65 (61, 70)	24 (18, 30)	57 (50, 64)
Difference from placebo (95% CI)	35 (28, 41)[d,e]		-	33 (24, 42)[d,e]	
Week 24	45 (40, 50)	73 (69, 78)	67 (63, 72)	20 (15, 26)	59 (53, 66)
Week 56		74 (70, 79)	69 (64, 73)		60 (53, 66)
ACR50, % of patients (95% CI)					
Week 12	13 (10, 17)	38 (33, 42)	38 (33, 42)	5 (2, 8)	32 (26, 38)
Week 24	19 (15, 23)	52 (48, 57)	44 (40, 49)	9 (6, 13)	38 (32, 45)
Week 56		60 (55, 64)	51 (47, 56)		41 (34, 47)
ACR70, % of patients (95% CI)					
Week 12	2 (1, 4)	16 (12, 19)	14 (11, 17)	1 (0, 1)	9 (5, 12)
Week 24	5 (3, 7)	29 (24, 33)	23 (19, 27)	1 (0, 2)	19 (14, 25)
Week 56		41 (36, 45)	31 (27, 36)		24 (18, 30)
MDA, % of patients (95% CI)					
Week 12	6 (4, 9)	25 (21, 29)	25 (21, 29)	4 (2, 7)	17 (12, 22)
Week 24	12 (9, 15)	37 (32, 41)[e]	33 (29, 38)	3 (1, 5)	25 (19, 31)[e]
Week 56		45 (40, 50)	40 (35, 44)		29 (23, 36)
Resolution of enthesitis (LEI=0), % of patients (95% CI)[a]					

Week 12	33 (27, 39)	47 (42, 53)	47 (41, 53)	20 (14, 27)	39 (31, 47)
Week 24	32 (27, 39)	54 (48, 60)[e]	47 (42, 53)	15 (9, 21)	43 (34, 51)
Week 56		59 (53, 65)	54 (48, 60)		43 (34, 51)
Resolution of dactylitis (LDI=0), % of patients (95% CI)[b]					
Week 12	42 (33, 51)	74 (66, 81)	72 (64, 80)	36 (24, 48)	64 (51, 76)
Week 24	40 (31, 48)	77 (69, 84)	74 (66, 82)	28 (17, 39)	58 (45, 71)
Week 56		75 (68, 82)	74 (66, 82)		51 (38, 64)
PASI75, % of patients (95% CI)[c]					
Week 16	21 (16, 27)	63 (56, 69)[e]	53 (46, 60)	16 (10, 22)	52 (44, 61)[e]
Week 24	27 (21, 33)	64 (58, 70)	59 (52, 65)	19 (12, 26)	54 (45, 62)
Week 56		65 (59, 72)	61 (55, 68)		52 (44, 61)
PASI90, % of patients (95% CI)[c]					
Week 16	12 (8, 17)	38 (32, 45)	39 (32, 45)	8 (4, 13)	35 (26, 43)
Week 24	17 (12, 22)	42 (35, 48)	45 (38, 52)	7 (3, 11)	36 (28, 44)
Week 56		49 (42, 56)	47 (40, 54)		41 (32, 49)

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement, ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; MDA = minimal disease activity; PASI75 (or 90) = ≥75% (or ≥90%) improvement in Psoriasis Area and Severity Index; PBO = placebo; UPA= upadacitinib

Patients who discontinued randomised treatment or were missing data at week of evaluation were imputed as non-responders in the analyses. For MDA, resolution of enthesitis, and resolution of dactylitis at week 24/56, the subjects rescued at week 16 were imputed as non-responders in the analyses.

[a] In patients with enthesitis at baseline (n=241, 270, and 265, respectively, for SELECT-PsA 1 and n=144 and 133, respectively, for SELECT-PsA 2)

[b] In patients with dactylitis at baseline (n=126, 136, and 127, respectively, for SELECT-PsA 1 and n=64 and 55, respectively, for SELECT-PsA 2)

[c] In patients with ≥ 3% BSA psoriasis at baseline (n=211, 214, and 211, respectively, for SELECT-PsA 1 and n=131 and 130, respectively, for SELECT-PsA 2)

[d] primary endpoint

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

[f] multiplicity-controlled p≤0.001 upadacitinib vs adalimumab comparison (non-inferiority test)

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 upadacitinib 15 mg resulted in statistically significant greater inhibition of the progression of structural joint damage compared to placebo at week 24 (Table 8). Erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0.5) was higher with upadacitinib 15 mg compared to placebo at week 24.

Table 8: Radiographic changes in SELECT-PsA 1

Treatment Group	PBO	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline (95% CI)			
Week 24	0.25 (0.13, 0.36)	-0.04 (-0.16, 0.07)[c]	0.01 (-0.11, 0.13)
Week 56[a]	0.44 (0.29, 0.59)	-0.05 (-0.20, 0.09)	-0.06 (-0.20, 0.09)
Proportion of patients with no radiographic progression[b], % (95% CI)			
Week 24	92 (89, 95)	96 (94, 98)	95 (93, 97)
Week 56[a]	89 (86, 92)	97 (96, 99)	94 (92, 97)
Abbreviations: ADA = adalimumab; PBO = placebo; UPA= upadacitinib [a] All placebo data at week 56 derived using linear extrapolation [b] No progression defined as mTSS change ≤0.5 [c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison			

Physical function response and health-related outcomes

In SELECT-PsA 1, patients treated with upadacitinib 15 mg showed statistically significant improvement from baseline in physical function as assessed by HAQ-DI at week 12 (-0.42 [95% CI: -0.47, -0.37]) compared to placebo (-0.14 [95% CI: -0.18, -0.09]); improvement in patients treated with adalimumab was -0.34 (95% CI: -0.38, -0.29). In SELECT-PsA 2, patients treated with upadacitinib 15 mg showed statistically significant improvement from baseline in HAQ-DI at week 12 (-0.30 [95% CI: -0.37, -0.24]) compared to placebo (-0.10 [95% CI: -0.16, -0.03]). Improvement in physical function was maintained through week 56 in both studies.

Health-related quality of life was assessed by SF-36v2. In both studies, patients receiving upadacitinib 15 mg experienced statistically significant greater improvement from baseline in the Physical Component Summary score compared to placebo at week 12. Improvements from baseline were maintained through week 56 in both studies.

Patients receiving upadacitinib 15 mg experienced statistically significant 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.

At baseline, psoriatic spondylitis was reported in 31% and 34% of patients in SELECT-PsA 1 and SELECT-PsA 2, respectively. Patients with psoriatic spondylitis treated with upadacitinib 15 mg showed improvements from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared to placebo at week 24. Improvements from baseline were maintained through week 56 in both studies.

Ankylosing spondylitis

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

SELECT-AXIS 1 was a 14-week trial in 187 ankylosing spondylitis patients with an inadequate response to at least two Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or intolerance to or contraindication for NSAIDs and had no previous exposure to biologic DMARDs. At baseline, patients had symptoms of ankylosing spondylitis for an average of 14.4 years and approximately 16% of the patients were on a concomitant csDMARD. Patients received upadacitinib 15 mg once daily or placebo. At week 14, all patients randomised to placebo were switched to upadacitinib 15 mg once

daily. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14.

Clinical response

In SELECT-AXIS 1, a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14 (Table 9). A numerical difference between treatment groups was observed at week 2 and response was maintained through week 64.

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

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

Table 9: Clinical response in SELECT-AXIS 1

Treatment Group	**PBO**	**UPA 15 mg**
N	94	93
ASAS40, % of patients (95% CI)[a]		
Week 14	25.5 (16.7, 34.3)	51.6 (41.5, 61.8)
Difference from placebo (95% CI)	26.1 (12.6, 39.5)[b,c]	
ASAS20, % of patients (95% CI)[a]		
Week 14	40.4 (30.5, 50.3)	64.5 (54.8, 74.2)[e]
ASAS Partial Remission, % of patients (95% CI)		
Week 14	1.1 (0.0, 3.1)	19.4 (11.3, 27.4)[c]
BASDAI 50, % of patients (95% CI)		
Week 14	23.4 (14.8, 32.0)	45.2 (35.0, 55.3)[d]
Change from baseline in ASDAS-CRP (95% CI)		
Week 14	-0.54 (-0.71, -0.37)	-1.45 (-1.62, -1.28)[c]
ASDAS Inactive Disease, % of patients (95% CI)		
Week 14	0	16.1 (8.7, 23.6)[e]
ASDAS Low Disease Activity, % of patients (95% CI)[f]		
Week 14	10.6 (4.4, 16.9)	49.5 (39.3, 59.6)[e]
ASDAS Major Improvement, % of patients (95% CI)		
Week 14	5.3 (0.8, 9.9)	32.3 (22.8, 41.8)[e]

Abbreviations: ASAS20 (or ASAS40) = Assessment of SpondyloArthritis international Society ≥20% (or ≥40%) improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PBO = placebo; UPA= upadacitinib

[a] An ASAS20 (ASAS40) response is defined as a ≥20% (≥40%) improvement and an absolute improvement from baseline of ≥1 (≥2) unit(s) (range 0 to 10) in ≥3 of 4 domains (Patient Global, Total Back Pain, Function, and Inflammation), and no worsening in the potential remaining domain (defined as worsening ≥20% and ≥1 unit for ASAS20 or defined as worsening of > 0 units for ASAS40).

[b] primary endpoint

[c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison

[d] multiplicity-controlled p≤0.01 upadacitinib vs placebo comparison

[e] comparison not multiplicity-controlled

[f] post-hoc analysis, not multiplicity-controlled

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 measures analysis.

Physical function response

Patients treated with upadacitinib 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by the BASFI at week 14.

Objective measure of inflammation

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

The efficacy and safety of upadacitinib 15 mg and 30 mg once daily was assessed in three Phase 3 randomised, double-blind, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 2584 patients (12 years of age and older). Upadacitinib was evaluated in 344 adolescent and 2240 adult patients with moderate to severe atopic dermatitis (AD) not adequately controlled by topical medication(s). At baseline, patients had to have all the following: an Investigator's Global Assessment (vIGA-AD) score ≥ 3 in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 (composite score assessing extent and severity of erythema, oedema/papulation, scratches and lichenification across 4 different body sites), a minimum body surface area (BSA) involvement of ≥ 10%, and weekly average Worst Pruritus Numerical Rating Scale (NRS) ≥ 4.

In all three studies, patients received upadacitinib once daily doses of 15 mg, 30 mg or matching placebo for 16 weeks. In the AD UP study, patients also received concomitant topical corticosteroids (TCS). Following completion of the double blinded period, patients originally randomised to upadacitinib were to continue receiving the same dose until week 260. Patients in the placebo group were re-randomised in a 1:1 ratio to receive upadacitinib 15 mg or 30 mg until week 260.

Baseline characteristics

In the monotherapy studies (MEASURE UP 1 and 2), 50.0% of patients had a baseline vIGA-AD score of 3 (moderate) and 50.0% of patients had a baseline vIGA-AD of 4 (severe). The mean baseline EASI score was 29.3 and the mean baseline weekly average Worst Pruritus NRS was 7.3. In the concomitant TCS study (AD UP), 47.1% of patients had a baseline vIGA-AD score of 3 (moderate) and 52.9% of patients had a baseline vIGA-AD of 4 (severe). The mean baseline EASI score was 29.7 and the mean baseline weekly average Worst Pruritus NRS was 7.2.

Clinical response

Monotherapy (MEASURE UP 1 AND MEASURE UP 2) and Concomitant TCS (AD UP) studies

A significantly greater proportion of patients treated with upadacitinib 15 mg or 30 mg achieved vIGA-AD 0 or 1, EASI 75, or a ≥ 4-point improvement on the Worst Pruritus NRS compared to placebo at week 16. Rapid improvements in skin clearance and itch were also achieved (see Table 10).

Figure 1 shows the proportion of patients achieving an EASI 75 response and mean percent change from baseline in Worst Pruritus NRS, respectively up to week 16 for MEASURE UP 1 and 2.

Table 10: Efficacy results of upadacitinib

Study	MEASURE UP 1			MEASURE UP 2			AD UP		
Treatment Group	PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg	PBO + TCS	UPA 15 mg + TCS	UPA 30 mg + TCS
Number of subjects randomised	281	281	285	278	276	282	304	300	297
Week 16 endpoints, % responders (95% CI)									
vIGA-AD 0/1[a,b] (co-primary)	8 (5,12)	48[d] (42,54)	62[d] (56,68)	5 (2,7)	39[d] (33,45)	52[d] (46,58)	11 (7,14)	40[d] (34,45)	59[d] (53,64)
EASI 75[a] (co-primary)	16 (12,21)	70[d] (64,75)	80[d] (75,84)	13 (9,17)	60[d] (54,66)	73[d] (68,78)	26 (21,31)	65[d] (59,70)	77[d] (72,82)
EASI 90[a]	8 (5,11)	53[d] (47,59)	66[d] (60,71)	5 (3,8)	42[d] (37,48)	58[d] (53,64)	13 (9,17)	43[d] (37,48)	63[d] (58,69)
EASI 100[a]	2 (0,3)	17[d] (12,21)	27[d] (22,32)	1 (0,2)	14[d] (10,18)	19[d] (14,23)	1 (0,3)	12[e] (8,16)	23[d] (18,27)
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	12 (8,16)	52[d] (46,58)	60[d] (54,66)	9 (6,13)	42[d] (36,48)	60[d] (54,65)	15 (11,19)	52[d] (46,58)	64[d] (58,69)
Early onset endpoints, % responders (95% CI)									
EASI 75[a] *(Week 2)*	4 (1,6)	38[d] (32,44)	47[d] (42,53)	4 (1,6)	33[d] (27,39)	44[d] (38,50)	7 (4,10)	31[d] (26,36)	44[d] (38,50)
Worst Pruritus NRS *(≥ 4-point improvement at week 1)*[c,f]	0 (0,1)	15[d] (11,19)	20[d] (15,24)	1 (0,2)	7[d] (4,11)	16[d] (11,20)	3 (1,5)	12[d] (8,16)	19[d] (15,24)

Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo

Subjects with rescue medication or with missing data were counted as non-responders. The number and percentage of subjects who were imputed as non-responders for EASI 75 and vIGA-AD 0/1 at Week 16 due to the use of rescue therapy in the placebo, upadacitinib 15 mg, and upadacitinib 30 mg groups, respectively, were 132 (47.0%), 31 (11.0%), 16 (5.6%) in MEASURE UP 1, 119 (42.8%), 24 (8.7%), 16 (5.7%) in MEASURE UP 2, and 78 (25.7%), 15 (5.0%), 14 (4.7%) in AD UP.

[a] Based on number of subjects randomised

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

[c] Results shown in subset of patients eligible for assessment (patients with Worst Pruritus NRS ≥ 4 at baseline)

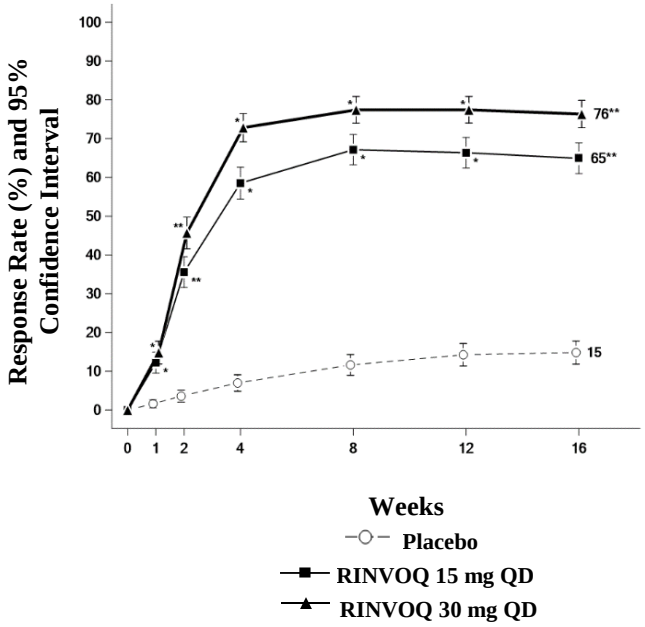
[d] Statistically significant vs. placebo with $p < 0.001$

[e] $p < 0.001$ vs placebo, without multiplicity control

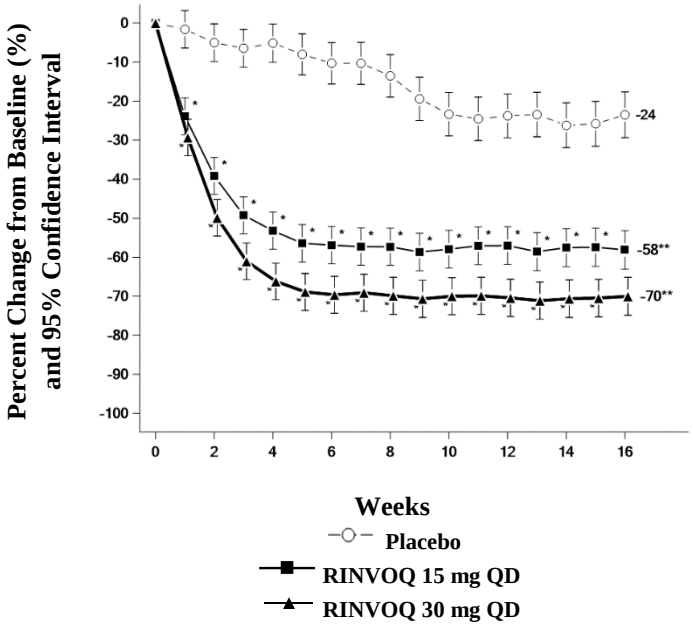
[f] Statistically significant improvements vs placebo were seen as early as 1 day after initiating upadacitinib 30 mg and 2 days after initiating upadacitinib 15 mg in MEASURE UP 1 and 2

Figure 1: Proportion of patients achieving an EASI 75 response and mean percent change from baseline in Worst Pruritus NRS in MEASURE UP 1 and MEASURE UP 2

Proportion of patients achieving an EASI 75 response



Mean percent change from baseline in Worst Pruritus NRS



*: $p < 0.001$ vs placebo, without multiplicity control
**: statistically significant vs. placebo with $p < 0.001$

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

Results at week 16 continued to be maintained through week 52 in patients treated with upadacitinib 15 mg or 30 mg.

Quality of life/patient-reported outcomes

Table 11: Patient-reported outcomes results of upadacitinib at week 16

Study	**MEASURE UP 1**			**MEASURE UP 2**		
Treatment group	PBO	UPA 15 mg	UPA 30 mg	PBO	UPA 15 mg	UPA 30 mg
Number of subjects randomised	281	281	285	278	276	282
% responders (95% CI)						
ADerm-SS Skin Pain *(≥ 4-point improvement)*[a]	15 (10,20)	54[e] (47,60)	63[e] (57,69)	13 (9,18)	49[e] (43,56)	65[e] (59,71)
ADerm-IS Sleep *(≥ 12-point improvement)* [a,b]	13 (9,18)	55[e] (48,62)	66[e] (60,72)	12 (8,17)	50[e] (44,57)	62[e] (56,69)
DLQI 0/1[c]	4 (2,7)	30[e] (25,36)	41[e] (35,47)	5 (2,7)	24[e] (19,29)	38[e] (32,44)
HADS Anxiety <8 and HADS Depression < 8[d]	14 (8,20)	46[e] (37,54)	49[e] (41,57)	11 (6,17)	46[e] (38,54)	56[e] (48,64)

Study	MEASURE UP 1	MEASURE UP 2
Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo; DLQI = Dermatology Life Quality Index; HADS = Hospital Anxiety and Depression Scale Subjects with rescue medication or with missing data were counted as non-responders. The threshold values specified correspond to the minimal clinically important difference (MCID) and was used to determine response. [a] Results shown in subset of patients eligible for assessment (patients with assessment score > MCID at baseline). [b] ADerm-IS Sleep assesses difficulty falling asleep, sleep impact, and waking up at night due to AD. [c] Results shown in subset of patients eligible for assessment (patients with DLQI > 1 at baseline). [d] Results shown in subset of patients eligible for assessment (patients with HADS Anxiety ≥ 8 or HADS Depression ≥ 8 at baseline) [e] Statistically significant vs. placebo with $p < 0.001$		

Paediatric population

A total of 344 adolescents aged 12 to 17 years with moderate to severe atopic dermatitis were randomised across the three Phase 3 studies to receive either 15 mg (N=114) or 30 mg (N=114) upadacitinib or matching placebo (N=116), in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the adolescents and adults. The safety profile in adolescents was generally similar to that in adults, with dose dependent increases in the rate of some adverse events, including neutropenia and herpes zoster. At both doses, the rate of neutropenia was slightly increased in adolescents compared to adults. The rate of herpes zoster in adolescents at the 30 mg dose was comparable to that in adults. The safety and efficacy of the 30 mg dose in adolescents are still being investigated.

Table 12: Efficacy results of upadacitinib for adolescents at week 16

Study	**MEASURE UP 1**		**MEASURE UP 2**		**AD UP**	
Treatment Group	PBO	UPA 15 mg	PBO	UPA 15 mg	PBO + TCS	UPA 15 mg + TCS
Number of adolescent subjects randomised	40	42	36	33	40	39
% responders (95% CI)						
vIGA-AD 0/1 [a,b]	8 (0,16)	38 (23,53)	3 (0,8)	42 (26,59)	8 (0,16)	31 (16,45)
EASI 75[a]	8 (0,17)	71 (58,85)	14 (3,25)	67 (51,83)	30 (16,44)	56 (41,72)
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	15 (4,27)	45 (30,60)	3 (0,8)	33 (16,50)	13 (2,24)	42 (26,58)

Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo
Subjects with rescue medication or with missing data were counted as non-responders.
[a] Based on number of subjects randomised
[b] Responder was defined as a patient with vIGA-AD 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 ordinal scale.
[c] Results shown in subset of patients eligible for assessment (patients with Worst Pruritus NRS ≥ 4 at baseline).

5.2 Pharmacokinetic properties

Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once-daily administrations.

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

Special populations

Renal impairment

Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild (estimated glomerular filtration rate 60 to 89 mL/min/1.73 m^2), moderate (estimated glomerular filtration rate 30 to 59 mL/min/1.73 m^2), and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m^2) renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function. Mild or moderate renal impairment has no clinically relevant effect on upadacitinib exposure following the 15 mg 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 (Child-Pugh C) hepatic impairment.

Paediatric population

The pharmacokinetics of upadacitinib have not yet been evaluated in paediatric patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (see section 4.2).

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

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

Intrinsic factors

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

5.3 Preclinical safety data

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

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

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

Upadacitinib had no effect on fertility in male or female rats at exposures up to approximately 21 and 43 times the maximum recommended human dose (MRHD) of 30 mg in males and females, respectively, on an AUC basis in a fertility and early embryonic development study.

Dose-related increases in foetal resorptions associated with post-implantation losses in this fertility study in rats were attributed to the developmental/teratogenic effects of upadacitinib. No adverse effects were observed at exposures below clinical exposure (based on AUC). Post-implantation losses were observed at exposures 11 times the clinical exposure at the MRHD of 30 mg (based on AUC).

In animal embryo-foetal development studies, upadacitinib was teratogenic in both rats and rabbits. Upadacitinib resulted in increases in skeletal malformations in rats at 1.6 and 0.8 times the clinical exposure (AUC-based) at the 15 and 30 mg (MRHD) doses, respectively. In rabbits an increased incidence of cardiovascular malformations was observed at 15 and 7.6 times the clinical exposure at the 15 and 30 mg doses (AUC-based), respectively. No developmental toxicity was observed at approximately 0.15 times (rat) and at similar exposure in rabbits as the exposures at the MRHD of 30 mg. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib

administration at exposures approximately 1.4 times the MRHD of 30 mg resulted in no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on the offspring.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet contents:

Microcrystalline cellulose
Mannitol
Hypromellose
Tartaric acid (powdered)
Magnesium stearate
Silica, colloidal anhydrous / Colloidal Silicon Dioxide

Film coating:

Polyvinyl alcohol
Macrogol /Polyethylene Glycol
Talc
Titanium dioxide (E171)
Black Iron oxide (E172) / Ferrosoferric Oxide (15 mg strength only)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store up to 30°C.
Store in the original blister or bottle in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

RINVOQ 15 mg prolonged-release tablets

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in packs containing 28 or 98 prolonged-release tablets, or multipacks containing 84 (3 packs of 28) prolonged-release tablets.

HDPE bottles with desiccant and polypropylene cap in carton containing 30 prolonged-release tablets. Pack size: 1 bottle (30 prolonged-release tablets) or 3 bottles (90 prolonged-release tablets).

Not all pack sizes may be marketed.

RINVOQ 30 mg prolonged-release tablets

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in packs containing 28 or 98 prolonged-release tablets.

HDPE bottles with desiccant and polypropylene cap in carton containing 30 prolonged-release tablets. Pack size: 1 bottle (30 prolonged-release tablets) or 3 bottles (90 prolonged-release tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany

8. LICENSE HOLDER

AbbVie biopharmaceuticals LTD., 4 Hacharash St., Hod Hasharon, Israel.

9. REGISTRATION NUMBER

164-29-36194
168-69-37036

Revised on April 2022 Based on MoH guidelines