דצמבר 2025

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

RINVOQ 15mg

Prolonged release tablets

(Upadacitinib 15mg as hemihydrate)

חברת AbbVie Biopharmaceuticals Ltd. שמחה להודיע על אישור התוויה חדשה לתכשיר רינבוק 15 מ"ג.

התכשיר מותווה לטיפול במחלות הבאות (נוסח ההתוויה המלא מצוי בעלון):

Rheumatoid arthritis, Psoriatic arthritis, Axial spondyloarthritis (Non-radiographic axial spondyloarthritis, Ankylosing spondylitis), Atopic dermatitis, Ulcerative colitis, Crohn's disease, Juvenile psoriatic arthritis & Polyarticular Juvenile Idiopathic Arthritis

התוויה חדשה לטיפול בדלקת עורקים של הרקה (Giant cell arteritis) במבוגרים.

נוסח ההתוויה החדשה שאושרה על ידי משרד הבריאות:

Giant cell arteritis

RINVOQ is indicated for the treatment of giant cell arteritis in adult patients.

בעקבות כך העלון לרופא והעלון לצרכן של התכשיר התעדכנו.

בנוסף העלון התעדכן עם מידע בטיחותי ומידע קליני חדש.

להודעה זו מצורפים עלונים עם סימון השינויים. מידע שהתווסף מסומן בכחול ומידע שהוסר מסומן ~~באדום~~.

העלון לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd, רחוב החרש 4, הוד השרון או בטלפון 09 – 7909600.

בברכה,
חברת אבווי ביופארמה בע"מ

RINVOQ®

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 MG
RINVOQ 30 MG
RINVOQ 45 MG
RINVOQ LQ

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.

RINVOQ 45 MG prolonged-release tablets

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

RINVOQ LQ oral solution

Each 1 ml contains upadacitinib (as hemihydrate), equivalent to 1 mg of upadacitinib.

Excipient with known effect
Each 1 ml of RINVOQ LQ oral solution contains 0.3 mg sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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’.

RINVOQ 45 MG prolonged-release tablets

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

RINVOQ LQ oral solution

Clear, colorless to light yellow solution.

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 15 MG 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 15 MG 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.

Axial spondyloarthritis

Non-radiographic axial spondyloarthritis (nr-axSpA)

RINVOQ 15 MG is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

RINVOQ 15 MG is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Giant cell arteritis

RINVOQ is indicated for the treatment of giant cell arteritis in adult patients.

Atopic dermatitis

RINVOQ 15 MG/RINVOQ 30 MG 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.

Ulcerative colitis

RINVOQ 15 MG/RINVOQ 30 MG/RINVOQ 45 MG is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Crohn's disease

RINVOQ 15 MG/RINVOQ 30 MG/RINVOQ 45 MG is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Juvenile psoriatic arthritis

RINVOQ 15 MG/ RINVOQ LQ is indicated for the treatment of patients 2 years of age and older with active juvenile psoriatic arthritis (JPsA) who have had an inadequate response or intolerance to one or more TNF blockers.

Limitations of Use:
RINVOQ 15 MG/RINVOQ LQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Polyarticular Juvenile Idiopathic Arthritis

RINVOQ 15 MG/RINVOQ LQ is indicated for the treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an inadequate response or intolerance to one or more TNF blockers.

Limitations of Use:
RINVOQ 15 MG/RINVOQ LQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

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 axial spondyloarthritis
The recommended dose of upadacitinib is 15 mg once daily.

Consideration should be given to discontinuing treatment in patients with axial spondyloarthritis 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.

Giant cell arteritis

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

Based upon the chronic nature of giant cell arteritis, upadacitinib 15 mg once daily can be continued as monotherapy following discontinuation of corticosteroids. Treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Patients who did not respond to IL-6 inhibitor treatment were not included in the study population.

Atopic dermatitis

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

- A dose of 15 mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy (see section 4.4)
- A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or patients with an inadequate response to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended dose is 15 mg once daily (see section 4.4).

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

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

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

Ulcerative colitis

Induction
The recommended induction dose of upadacitinib is 45 mg once daily (one tablet of 45 mg or three tablets of 15 mg) for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, upadacitinib 45 mg once daily may be continued for an additional 8 week period (see section 5.1). Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance
The recommended maintenance dose of upadacitinib is 15 mg (one tablet of 15 mg) or 30 mg (one tablet of 30 mg or two tablets of 15 mg) once daily based on individual patient presentation:

- A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy (see section 4.4).
- A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended dose is 15 mg once daily (see section 4.4).

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

Crohn's disease

Induction
The recommended induction dose of upadacitinib is 45 mg once daily (one tablet of 45 mg or three tablets of 15 mg) for 12 weeks. For patients who have not achieved adequate therapeutic benefit after the initial 12-week induction, prolonged induction for an additional 12 weeks with a dose of 30 mg (one tablet of 30 mg or two tablets of 15 mg) once daily may be considered. For these patients, upadacitinib should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment.

Maintenance
The recommended maintenance dose of upadacitinib is 15 mg (one tablet of 15 mg) or 30 mg (one tablet of 30 mg or two tablets of 15 mg) once daily based on individual patient presentation:

- A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy (see section 4.4).
- A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended maintenance dose is 15 mg once daily (see section 4.4).

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

Juvenile psoriatic arthritis and Polyarticular Juvenile Idiopathic Arthritis
The recommended dosage for patients 2 years and older is based on body weight.

Patient weight 10 kg to less than 20 kg:
RINVOQ LQ 3 mg (3 mL oral solution) twice daily.
RINVOQ 15 MG is not recommended.

Patient weight 20 kg to less than 30 kg:
RINVOQ LQ 4 mg (4 mL oral solution) twice daily.
RINVOQ 15 MG is not recommended.

Patient weight 30 kg and greater:
RINVOQ LQ 6 mg (6 mL oral solution) twice daily.
RINVOQ 15 MG (one 15 mg tablet) once daily.

RINVOQ LQ oral solution is not substitutable with RINVOQ prolonged-release tablets. Changes between RINVOQ LQ oral solution and RINVOQ prolonged-release tablets should be made by the health care provider.

Interactions

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

Dose initiation

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

Dose interruption

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

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

Table 1 Laboratory measures and monitoring guidance

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

Special populations

Elderly

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis
There are limited data in patients 75 years of age and older (see section 4.4).

Atopic dermatitis
For atopic dermatitis, doses higher than 15 mg once daily are not recommended in patients 65 years of age and older (see sections 4.4 and 4.8).

Ulcerative colitis and Crohn's disease
For ulcerative colitis *and Crohn's disease*, doses higher than 15 mg once daily for maintenance therapy are not recommended in patients 65 years of age and older (see sections 4.4 and 4.8). The safety and efficacy of upadacitinib in patients 75 years of age and older have not yet been established.

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 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 as described in Table 2. The use of upadacitinib has not been studied in subjects with end stage renal disease and is therefore not recommended for use in these patients.

Table 2 Recommended dose for severe renal impairment[a]

Therapeutic indication	Recommended once daily dose
Rheumatoid arthritis, Psoriatic arthritis, Axial spondyloarthritis, giant cell arteritis, Atopic dermatitis	15 mg
Ulcerative colitis, Crohn's disease	Induction: 30 mg
	Maintenance: 15 mg
Polyarticular juvenile idiopathic arthritis, Juvenile psoriatic arthritis	No dose adjustment required
[a]estimated glomerular filtration rate (eGFR) 15 to < 30 ml/min/1.73m^2	

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.

The safety and efficacy of RINVOQ LQ in children with atopic dermatitis have not been established. The safety and efficacy of RINVOQ/RINVOQ LQ in children and adolescents with axial spondyloarthritis, ulcerative colitis, and Crohn's disease, aged 0 to less than 18 years have not yet been established. No data are available.

There is no relevant use of RINVOQ in the paediatric population in the indication giant cell arteritis.

Polyarticular Juvenile Idiopathic Arthritis and Juvenile Psoriatic Arthritis
The safety and efficacy of RINVOQ 15 MG/RINVOQ LQ in paediatric patients 2 to less than 18 years of age with pJIA and JPsA have been established.

The use of RINVOQ 15 MG/RINVOQ LQ in these age groups is supported by evidence from well-controlled studies of RINVOQ in adults with rheumatoid arthritis and psoriatic arthritis, pharmacokinetic data from adult patients with rheumatoid arthritis and psoriatic arthritis and 51 paediatric patients with JIA with active polyarthritis, and safety data from 83 paediatric patients 2 to < 18 years of age with JIA with active polyarthritis. Upadacitinib plasma exposures in paediatric patients with pJIA and JPsA at the recommended dosage are predicted to be comparable to those observed in adults with rheumatoid arthritis and psoriatic arthritis based on population pharmacokinetic modeling and simulation.

The safety and efficacy of RINVOQ/RINVOQ LQ in paediatric patients less than 2 years of age with pJIA or JPsA have not been established.

Method of administration

RINVOQ tablets are 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.

RINVOQ LQ oral solution is to be taken twice daily with or without food.

RINVOQ LQ oral solution is not substitutable with RINVOQ prolonged-release tablets.
Changes between RINVOQ LQ oral solution and RINVOQ prolonged-release tablets should be made by the health care provider.

RINVOQ LQ oral solution should be administered using the provided press-in bottle adapter and oral dosing syringe.

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

Upadacitinib should only be used if no suitable treatment alternatives are available in patients:
- 65 years of age and older;
- patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
- patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Use in patients 65 years of age and older

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

In patients 65 years of age and older, there is an increased risk of adverse reactions with upadacitinib 30 mg once daily. Consequently, the recommended dose for long-term use in this patient population is 15 mg once daily (see sections 4.2 and 4.8).

Immunosuppressive medicinal products

Combination with other potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin, tacrolimus, and biologic DMARDs or other JAK inhibitors has not been evaluated in clinical studies and is not recommended as a risk of additive immunosuppression cannot be excluded.

Serious infections

Serious and sometimes fatal infections have been reported in patients receiving upadacitinib. The most frequent serious infections reported with upadacitinib included pneumonia (see section 4.8) and cellulitis. Cases of bacterial meningitis and sepsis 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 (see section 4.3).

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.

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

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients 65 years of age and older, upadacitinib should only be used if no suitable treatment alternatives are available (see section 4.2).

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 treatment, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines (see section 5.1).

Malignancy

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib.

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

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

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

Non-melanoma skin cancer (NMSC)

NMSCs have been reported in patients treated with upadacitinib (see section 4.8). A higher rate of NMSC was observed with upadacitinib 30 mg compared to upadacitinib 15 mg. Periodic skin examination is recommended for all patients, particularly those with risk factors 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).

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

Upadacitinib should be used with caution in patients who may be at risk for gastrointestinal perforation (e.g., patients with diverticular disease, a history of diverticulitis, or who are taking nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids or opioids). Patients with active Crohn's disease are at increased risk for developing intestinal perforation Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

Major adverse cardiovascular events

Events of MACE were observed in clinical studies of upadacitinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate

of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors.

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

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 (see section 4.8).

Hepatic transaminases must be evaluated 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) were observed in clinical trials for upadacitinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose-dependent higher rate of VTE including DVT and PE was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events” and “Malignancy”) upadacitinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, upadacitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. Patients should be re-evaluated periodically during upadacitinib treatment to assess for changes in VTE risk. Patients with signs and symptoms of VTE should be promptly evaluated and treatment should be discontinued in patients with suspected VTE, regardless of dose.

Retinal vein occlusion

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

Hypersensitivity reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema have been reported in patients receiving upadacitinib. If a clinically significant hypersensitivity reaction occurs, treatment with upadacitinib must be discontinued and appropriate therapy must be instituted (see sections 4.3 and 4.8).

Hypoglycaemia in patients treated for diabetes

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

Medication Residue in Stool

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

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

Excipients with known effect

RINVOQ LQ oral solution contains 0.3 mg sodium benzoate in each mL.

RINVOQ LQ oral solution contains less than 1 mmol sodium (23 mg) per dose, essentially 'sodium-free'.

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.

Co-administration with CYP3A4 inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, and grapefruit). In a clinical study, co-administration of upadacitinib tablets with ketoconazole resulted in 70% and 75% increases in upadacitinib C_{max} and AUC, respectively. Upadacitinib oral solution and 15 mg tablets should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. Upadacitinib 30 mg tablet once daily dose is not recommended for patients with atopic dermatitis receiving chronic treatment with strong CYP3A4 inhibitors. For patients with ulcerative colitis or Crohn's disease using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg tablet once daily and the recommended maintenance dose is 15 mg tablet once daily (see section 4.2). Alternatives to strong CYP3A4 inhibitors should be considered when used in the long-term. Food or drink containing grapefruit should be avoided during treatment with upadacitinib.

Co-administration 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, co-administration of upadacitinib tablets after multiple doses of rifampicin (strong CYP3A inducer) resulted in approximately 50% and 60% decreases in upadacitinib C_{max} and AUC, respectively. Patients should be monitored for changes in disease activity if upadacitinib is co-administered with strong CYP3A4 inducers.

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

Potential for upadacitinib to affect the pharmacokinetics of other medicinal products

Administration of multiple 30 mg or 45 mg once daily doses of upadacitinib tablets to healthy subjects had a limited effect on midazolam (sensitive substrate for CYP3A) plasma exposures (24-26% decrease in midazolam AUC and C_{max}), indicating that upadacitinib 30 mg or 45 mg once daily may have a weak induction effect on CYP3A. In a clinical study, rosuvastatin and atorvastatin AUC were decreased by 33% and 23%, respectively, and rosuvastatin C_{max} was decreased by 23% following the administration of multiple 30 mg once daily doses of upadacitinib tablets to healthy subjects. Upadacitinib had no relevant effect on atorvastatin C_{max} or on plasma exposures of ortho-hydroxyatorvastatin (major active metabolite for atorvastatin). Administration of multiple 45 mg once daily doses of upadacitinib tablets to healthy subjects led to a limited increase in AUC and C_{max} of dextromethorphan (sensitive CYP2D6 substrate) by 30% and 35%, respectively, indicating that upadacitinib 45 mg once daily has a weak inhibitory effect on CYP2D6. No dose adjustment is recommended for CYP3A substrates, CYP2D6 substrates, rosuvastatin or atorvastatin when co-administered with upadacitinib.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have 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 may have a minor influence on the ability to drive and use machines because dizziness and vertigo may occur during treatment with RINVOQ (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In the placebo-controlled clinical trials for rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, 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%), neutropenia (2.8%), 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%), blood 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%).

In the placebo-controlled ulcerative colitis and Crohn's disease induction and maintenance clinical trials, the most commonly reported adverse reactions (≥3% of patients) with upadacitinib 45 mg, 30 mg or 15 mg were upper respiratory tract infection (19.9%), pyrexia (8.7%), blood CPK increased (7.6%), anaemia (7.4%), headache (6.6%), acne (6.3%), herpes zoster (6.1%), neutropenia (6.0%), rash (5.2%), pneumonia (4.1%), hypercholesterolemia (4.0%), bronchitis (3.9%), aspartate transaminase increased (3.9%), fatigue (3.9%), folliculitis (3.6%), alanine transaminase increased (3.5%), herpes simplex (3.2%), and influenza (3.2%).

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 and post-marketing experience.The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100). The frequencies in Table 3 are based on the higher of the rates for adverse reactions reported with RINVOQ in clinical trials of rheumatologic disease (15 mg), ~~-~~atopic dermatitis (15 mg and 30 mg), ulcerative colitis (15 mg, 30 mg and 45 mg)~~-~~, or Crohn's disease (15 mg, 30 mg, and 45 mg). When notable differences in frequency were observed between indications, these are presented in the footnotes below the table.

Table 3 Adverse reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)[a]	Bronchitis[a,b] Herpes zoster[a] Herpes simplex[a] Folliculitis Influenza Urinary tract infection Pneumonia[a,h]	Oral candidiasis Diverticulitis Sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancer[f]	
Blood and lymphatic system disorders		Anaemia[a] Neutropenia[a] Lymphopenia	
Immune system disorders		Urticaria[c,g]	Serious hypersensitivity reactions[a,e]
Metabolism and nutrition disorders		Hypercholesterolaemia[a], [b] Hyperlipidaemia[a,b]	Hypertriglyceridaemia
Nervous system disorders		Headache[a,j] Dizziness	
Ear and labyrinth disorders		Vertigo[a]	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Abdominal pain[a] Nausea	Gastrointestinal perforation[i]
Skin and subcutaneous tissue disorders	Acne[a,c,d,g]	Rash[a]	
General disorders and administration site conditions		Fatigue Pyrexia Peripheral oedema[a,k]	
Investigations		Blood CPK increased ALT increased[b] AST increased[b] Weight increased[g]	

[a] Presented as grouped term
[b] In atopic dermatitis trials, the frequency of bronchitis, hypercholesterolaemia, hyperlipidaemia, ALT increased, and AST increased was uncommon.
[c] In rheumatologic disease trials, the frequency was common for acne and uncommon for urticaria.
[d] In ulcerative colitis trials, the frequency was common for acne.
[e] Serious hypersensitivity reactions including anaphylactic reaction and angioedema
[f] Most events reported as basal cell carcinoma and squamous cell carcinoma of skin
[g] In Crohn's disease, the frequency was common for acne, and uncommon for urticaria and weight increased.
[h] Pneumonia was common in Crohn's disease and uncommon across other indications.
[i] Frequency is based on Crohn's disease clinical trials.
[j] Headache was very common in the giant cell arteritis trial.
[k] Frequency is based on the giant cell arteritis trial.

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 (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 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. Of the 22 cases of hepatic transaminase elevations, most were asymptomatic and transient.

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

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

Lipid elevations

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

limits on at least one occasion during 12/14 weeks (including patients who had an isolated elevated value):

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

Creatine phosphokinase

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

Neutropenia

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

Psoriatic arthritis

Overall, the safety profile observed in patients with active psoriatic arthritis treated with upadacitinib 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher 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.

Axial spondyloarthritis

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

Giant cell arteritis

Overall, the safety profile observed in patients with giant cell arteritis treated with upadacitinib 15 mg was generally consistent with the known safety profile for upadacitinib.

Serious Infections

In the placebo-controlled clinical study, the frequency of serious infections over 52 weeks was 5.7% in the upadacitinib 15 mg group and 10.7% in the placebo group. The long-term rate of serious infections for the upadacitinib 15 mg group was 2.9 events per 100 patient-years.

Opportunistic infections (excluding tuberculosis)

In the placebo-controlled clinical study, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) over 52 weeks was 1.9% in the upadacitinib 15 mg group and 0.9% in the placebo group. The long-term rate of opportunistic infections (excluding tuberculosis and herpes zoster) for the upadacitinib 15 mg group was 0.6 events per 100 patient-years.

In the placebo-controlled clinical study, the frequency of herpes zoster over 52 weeks was 5.3% in the upadacitinib 15 mg group and 2.7% in the placebo group. The long-term rate of herpes zoster for the upadacitinib 15 mg group was 4.1 events per 100 patient-years.

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. At week 52, the mean increase in LDL cholesterol from baseline was 0.41 mmol/L for upadacitinib 15 mg and 0.56 mmol/L for upadacitinib 30 mg.

Ulcerative colitis

The overall safety profile observed in patients with ulcerative colitis was generally consistent with that observed in patients with rheumatoid arthritis.

A higher rate of herpes zoster was observed with an induction treatment period of 16 weeks vs 8 weeks.

Infections

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

In the placebo-controlled induction studies, the frequency of serious infection over 8 weeks in both the upadacitinib 45 mg group and the placebo group was 1.3%. No additional serious infections were observed over 8-week extended treatment with upadacitinib 45 mg. In the placebo-controlled maintenance study, the frequency of serious infection over 52 weeks in the upadacitinib 15 mg and 30 mg groups was 3.6% and 3.2%, respectively, compared to 3.3% in the placebo group. The long-term rate of serious infections for the upadacitinib 15 mg and 30 mg groups was 3.0 and 4.6 events per 100 patient-years, respectively. The most frequently reported serious infection in the induction and maintenance phases was COVID-19 pneumonia.

Opportunistic infections (excluding tuberculosis)

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

In the placebo-controlled induction studies over 8 weeks, the frequency of herpes zoster in the upadacitinib 45 mg group was 0.6% and 0% in the placebo group. The frequency of herpes zoster was 3.9% over 16-week treatment with upadacitinib 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of herpes zoster in the upadacitinib 15 mg and 30 mg groups was 4.8% and 5.6%, respectively, compared to 0% in the placebo group. The long-term rate of herpes zoster for the upadacitinib 15 mg and 30 mg groups was 4.5 and 7.2 events per 100 patient-years, respectively.

Gastrointestinal perforations

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

Laboratory abnormalities

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

In the placebo-controlled induction studies for up to 8 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 2.0% and 0.8% of patients in the upadacitinib 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 1.6%, 1.2% and 0.8% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ALC < 0.5 x 10^9 cells/L (see section 4.2). No notable mean changes of lymphocyte counts were observed during upadacitinib treatment over time.

Elevations in lipid parameters were observed at 8 weeks of treatment with upadacitinib 45 mg and remained generally stable with longer-term treatment with upadacitinib 15 mg and 30 mg. Among patients in the placebo-controlled induction studies with baseline values below the specified limits, the following frequencies of patients were observed to shift to above the specified limits on at least one occasion during 8 weeks (including patients who had an isolated elevated value):

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

Crohn's disease

Overall, the safety profile observed in patients with Crohn's disease treated with upadacitinib was consistent with the known safety profile for upadacitinib.

Serious infections

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

Gastrointestinal perforations

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

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

Laboratory abnormalities

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

In the placebo-controlled induction studies for up to 12 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 2.2% and 2.0% of patients in the upadacitinib 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 4.6%, 5.2% and 1.8% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ALC < 0.5 x 10^9 cells/L (see section 4.2). No notable mean changes of lymphocyte counts were observed during upadacitinib treatment over time.

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

Elderly

Based on the limited data from patients 65 years and older with atopic dermatitis, ulcerative colitis and Crohn's disease, there was a higher rate of overall adverse reactions with the upadacitinib 30 mg dose compared to the 15 mg dose (see section 4.4).

Paediatric population

Atopic Dermatitis

A total of 541 adolescents aged 12 to 17 years with atopic dermatitis were treated in the global Phase 3 studies and the supplemental adolescent substudies, of whom 264 were exposed to 15 mg. The safety profile for upadacitinib 15 mg in adolescents was similar to that in adults. With long-term exposure, the adverse drug reaction of skin papilloma was reported in 3.4% of adolescent patients with atopic dermatitis treated with upadacitinib 15 mg.

Polyarticular Juvenile Idiopathic Arthritis

A total of 83 paediatric patients with juvenile idiopathic arthritis (JIA) with active polyarthritis were treated with upadacitinib in the clinical trial, representing 123.7 patient-years of exposure, of whom 48 were exposed to upadacitinib for at least one year.

Overall, the safety profile observed in paediatric patients with JIA with active polyarthritis treated with upadacitinib was consistent with the known safety profile of upadacitinib.

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, Janus-associated kinase (JAK) inhibitors
ATC code: L04AF03

Mechanism of action

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

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

Pharmacodynamic effects

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

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

Lymphocytes

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

hsCRP

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

Vaccine studies

The influence of upadacitinib on the humoral response following administration of adjuvanted recombinant glycoprotein E herpes zoster vaccine was evaluated in 93 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg tablets. 98% of patients were on concomitant methotrexate. 49% of patients were on oral corticosteroids at baseline. The primary endpoint was the proportion of patients with a satisfactory humoral response defined as ≥ 4-fold increase in pre-vaccination concentration of anti-glycoprotein E titer levels at week 16 (4 weeks post-dose 2 vaccination). Vaccination of patients treated with upadacitinib 15 mg tablets resulted in a satisfactory humoral response in 79/90 (88% [95% CI: 81.0, 94.5]) of patients at week 16.

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) tablets. 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 tablets, 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 4). Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. Four studies included long-term extensions for up to 5 years, and one study (SELECT-COMPARE) included a long-term extension for up to 10 years.

The primary analysis for each of these studies included all randomised subjects who received at least 1 dose of 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 4 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 5). 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. At 3 years, 297/651 (45.6%) and 111/327 (33.9%) patients remained on originally randomised treatment of upadacitinib 15 mg or adalimumab, respectively, in SELECT-COMPARE, and 216/317 (68.1%) and 149/315 (47.3%) patients remained on originally randomised treatment of upadacitinib 15 mg or MTX monotherapy, respectively, in SELECT-EARLY. Among the patients who remained on their originally allocated treatment, low disease activity and clinical remission were maintained through 3 years.

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 5). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained through 3 years among the patients who remained on their originally allocated treatment.

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 5 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 6). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with upadacitinib 15 mg in both studies. Inhibition of progression of structural joint damage was maintained through week 96 in both studies for patients who remained on their originally allocated treatment with upadacitinib 15 mg (based on available results from 327 patients in SELECT-COMPARE and 238 patients in SELECT-EARLY).

Table 6 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 7). Improvement in HAQ-DI was maintained through 3 years for patients who remained on their originally allocated treatment with upadacitinib 15 mg based on available results from SELECT-COMPARE and SELECT-EARLY.

Table 7 Mean change from baseline in HAQ-DI[a,b]

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

Abbreviations: ADA = adalimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA = upadacitinib
[a] Data shown are mean
[b] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[c] SELECT-EARLY, SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND
[d] SELECT-MONOTHERAPY
[e] SELECT-EARLY
[f] SELECT-COMPARE
[g] multiplicity-controlled p≤0.001 upadacitinib vs placebo or MTX comparison
[h] nominal p≤0.001 upadacitinib vs placebo or MTX comparison
[i] nominal p≤0.01 upadacitinib vs adalimumab comparison

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, multicentre, 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 8). 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 8 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 9). 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 9 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.

Axial spondyloarthritis

Non-radiographic axial spondyloarthritis

The efficacy and safety of upadacitinib 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 non-radiographic axial spondyloarthritis. Study SELECT-AXIS 2 (nr-axSpA) was a 52-week placebo-controlled trial in 314 patients with active non-radiographic axial spondyloarthritis with an inadequate response to at least two NSAIDs or intolerance to or contraindication for NSAIDs. Patients must have had objective signs of inflammation indicated by elevated C-reactive protein (CRP) (defined as > upper limit of normal), and/or sacroiliitis on magnetic resonance imaging (MRI), and no definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 numerical rating scale (NRS) at the Screening and Baseline

Visits. At baseline, patients had symptoms of non-radiographic axial spondyloarthritis for an average of 9.1 years and 29.1% of the patients were on a concomitant csDMARD. 32.9% of the patients had an inadequate response or intolerance to bDMARD therapy. Patients received upadacitinib 15 mg once daily or placebo. At week 52, 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. The study included a long-term extension for up to 2 years. Of patients who were initially randomised to upadacitinib, 75% (117/156) in SELECT-AXIS 2 (nr-axSpA) continued therapy through 2 years.

Clinical response

In SELECT-AXIS 2 (nr-axSpA), a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14 (Table 10).
A numerical difference between treatment groups was observed at all timepoints from week 2 to week 14.
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, compared to placebo at week 14.

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

Table 10 Clinical response in SELECT-AXIS 2 (nr-axSpA)

Treatment Group	**PBO**	**UPA 15 mg**
N	157	156
ASAS40, % of patients (95% CI) [a]		
Week 14	22.5 (16.0, 29.1)	44.9 (37.1, 52.7)
Difference from placebo (95% CI)	22.2 (12.1, 32.3)[b]	
Week 52	42.7 (34.9, 50.4)	62.8 (55.2, 70.4)[d]
ASAS20, % of patients (95% CI) [a]		
Week 14	43.8 (36.0, 51.5)	66.7 (59.3, 74.1)[b]
ASAS Partial Remission, % of patients (95% CI)		
Week 14	7.6 (3.5, 11.8)	18.6 (12.5, 24.7)[c]
BASDAI 50, % of patients (95% CI)		
Week 14	22.1 (15.5, 28.6)	42.3 (34.6, 50.1)[b]
Change from baseline in ASDAS-CRP (95% CI)		
Week 14	-0.71 (-0.85, -0.56)	-1.36 (-1.50, -1.21)[b]
ASDAS Inactive Disease, % of patients (95% CI)		
Week 14	5.2 (1.7, 8.7)	14.1 (8.6, 19.6)[c]
ASDAS Low Disease Activity, % of patients (95% CI)		
Week 14	18.3 (12.2, 24.4)	42.3 (34.6, 50.1)[b]

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] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison

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

[d] Nominal p≤0.001 for upadacitinib vs placebo comparison, according to prespecified multiplicity-controlled testing sequence
For binary endpoints, results are based on non-responder imputation in conjunction with multiple imputation. For continuous endpoints, results are based on the least squares mean change from baseline using mixed-effect models repeated measures analysis.

Efficacy was maintained through 2 years as assessed by the endpoints presented in Table 10.

Physical function response and health-related outcomes

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.

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

Patients treated with upadacitinib 15 mg showed significant improvements in health-related quality of life and overall health as measured by ASQoL and ASAS Health Index, respectively, compared to placebo at week 14.

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

Objective measure of inflammation

Signs of inflammation were assessed by MRI and expressed as change from baseline in the Spondyloarthritis Research Consortium of Canada (SPARCC) score of the sacroiliac joints. At week 14, significant improvement of inflammatory signs in the sacroiliac joints was observed in patients treated with upadacitinib 15 mg compared to placebo. Improvement in inflammation as assessed by MRI was maintained through 2 years.

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

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

SELECT-AXIS 1 was a 14-week placebo-controlled trial in 187 ankylosing spondylitis patients with an inadequate response to at least two 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.

SELECT-AXIS 2 (AS) was a 14-week placebo-controlled trial in 420 ankylosing spondylitis patients with prior exposure to bDMARDs (77.4% had lack of efficacy to either a TNF inhibitor or interleukin-17 inhibitor (IL-17i); 30.2% had intolerance; 12.9% had prior exposure but not lack of efficacy to two bDMARDs). At baseline, patients had symptoms of ankylosing spondylitis for an average of 12.8 years and approximately 31% 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.

Of patients who were initially randomised to upadacitinib, 72% (67/93) in SELECT-AXIS 1 and 77% (163/211) in SELECT-AXIS 2 (AS) continued therapy through 2 years.

Clinical response

In both studies, a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14 (Table 11). A numerical difference between treatment groups was observed from week 2 in SELECT-AXIS 1 and week 4 in SELECT-AXIS 2 (AS) for ASAS40.

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, baseline hsCRP, and prior use of bDMARDs.

Table 11 Clinical response

Study	**SELECT-AXIS 1 bDMARD-naïve**		**SELECT-AXIS 2 (AS) bDMARD-IR**	
Treatment Group	**PBO**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
N	94	93	209	211
ASAS40, % of patients (95% CI)[a,b]				
Week 14	25.5 (16.7, 34.3)	51.6 (41.5, 61.8)	18.2 (13.0, 23.4)	44.5 (37.8, 51.3)
Difference from placebo (95% CI)	26.1 (12.6, 39.5)[c]		26.4 (17.9, 34.9)[c]	
ASAS20, % of patients (95% CI)[a]				
Week 14	40.4 (30.5, 50.3)	64.5 (54.8, 74.2)[e]	38.3 (31.7, 44.9)	65.4 (59.0, 71.8)[c]
ASAS Partial Remission, % of patients (95% CI)				
Week 14	1.1 (0.0, 3.1)	19.4 (11.3, 27.4)[c]	4.3 (1.6, 7.1)	17.5 (12.4, 22.7)[c]
BASDAI 50, % of patients (95% CI)				
Week 14	23.4 (14.8, 32.0)	45.2 (35.0, 55.3)[d]	16.7 (11.7, 21.8)	43.1 (36.4, 49.8)[c]
Change from baseline in ASDAS-CRP (95% CI)				
Week 14	-0.54 (-0.71, -0.37)	-1.45 (-1.62, -1.28)[c]	-0.49 (-0.62, -0.37)	-1.52 (-1.64, -1.39)[c]
ASDAS Inactive Disease, % of patients (95% CI)				
Week 14	0	16.1 (8.7, 23.6)[e]	1.9 (0.1, 3.8)	12.8 (8.3, 17.3)[c]
ASDAS Low Disease Activity, % of patients (95% CI)				
Week 14	10.6 (4.4, 16.9)	49.5 (39.3, 59.6)[f]	10.1 (6.0, 14.2)	44.1 (37.4, 50.8)[c]
ASDAS Major Improvement, % of patients (95% CI)				
Week 14	5.3 (0.8, 9.9)	32.3 (22.8, 41.8)[e]	4.8 (1.9, 7.7)	30.3 (24.1, 36.5)[e]

[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 for SELECT-AXIS 1, not multiplicity-controlled
For binary endpoints, week 14 results are based on non-responder imputation (SELECT-AXIS 1) and on non-responder imputation in conjunction with multiple imputation (SELECT-AXIS 2 [AS]). For continuous endpoints, week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis.

In both studies, efficacy was maintained through 2 years as assessed by the endpoints presented in Table 11.

Physical function response and health-related outcomes

In both studies, patients treated with upadacitinib 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) change from baseline at week 14. Improvement in BASFI was maintained through 2 years.

In SELECT-AXIS 2 (AS), patients treated with upadacitinib 15 mg showed significant improvements in total back pain and nocturnal back pain compared to placebo at week 14. Improvements in total back pain and nocturnal back pain were maintained through 2 years.

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

Enthesitis
In SELECT-AXIS 2 (AS), patients with pre-existing enthesitis (n=310) treated with upadacitinib 15 mg showed significant improvement in enthesitis compared to placebo as measured by change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at week 14. Improvement in enthesitis was maintained through 2 years.

Spinal mobility
In SELECT-AXIS 2 (AS), patients treated with upadacitinib 15 mg showed significant improvement in spinal mobility compared to placebo as measured by change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) at week 14. Improvement in BASMI was maintained through 2 years.

Objective measure of inflammation

Signs of inflammation were assessed by MRI and expressed as change from baseline in the SPARCC score for spine. In both studies, at week 14, significant improvement of inflammatory signs in the spine was observed in patients treated with upadacitinib 15 mg compared to placebo. Improvement in inflammation as assessed by MRI was maintained through 2 years.

Giant cell arteritis

The efficacy and safety of upadacitinib 15 mg once daily were assessed in SELECT-GCA, a Phase 3 randomised, double-blind, multicentre, placebo-controlled study in patients 50 years of age and older with new onset or relapsing giant cell arteritis. Patients who did not respond to IL-6 inhibitor treatment were not included in the study population.

SELECT-GCA was a 52-week study in which 428 patients were randomised in a 2:1:1 ratio and dosed once daily with upadacitinib 15 mg, upadacitinib 7.5 mg, or placebo. All patients received background corticosteroid (prednisone or prednisolone) therapy. The upadacitinib-treated groups followed a pre-specified corticosteroid taper regimen with the aim to reach 0 mg by 26 weeks; the placebo-treated group followed a pre-specified corticosteroid taper regimen with the aim to reach 0 mg by 52 weeks. The primary endpoint was the proportion of patients achieving sustained remission at week 52 as defined by the absence of giant cell arteritis signs and symptoms from week 12 through week 52 and adherence to the protocol-defined corticosteroid taper regimen. Patients who prematurely discontinued study treatment (upadacitinib or placebo) or had a missing assessment were classified as non-responders. The study included a 52-week extension for a total study duration of up to 2 years.

Clinical response

Upadacitinib 15 mg and a 26-week corticosteroid taper showed superiority in achieving corticosteroid-free sustained remission at week 52 compared to placebo and a 52-week corticosteroid taper (Table 12). Results for each component of sustained remission and sustained complete remission at week 52 were consistent with those of the composite endpoints. For sustained remission at week 52 (the primary endpoint), a similar percentage of patients in each arm were classified as non-responders due to premature discontinuation of study treatment (placebo: 19.6%; upadacitinib 15 mg: 20.1%) or due to a missing assessment (placebo: 0.9%; upadacitinib 15 mg: 0.5%).

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

A significantly lower proportion of patients treated with upadacitinib 15 mg and a 26-week corticosteroid taper experienced at least one giant cell arteritis flare compared to those treated with placebo and a 52-week corticosteroid taper through week 52. In addition, the risk of flare in the upadacitinib arm was significantly lower compared to the placebo arm as measured by time to first flare through week 52 (Table 12).

Table 12 Clinical response in SELECT-GCA

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

Abbreviations: ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; hsCRP = high sensitivity C-reactive protein; PBO = placebo; UPA = upadacitinib

[a] Sustained remission is defined as having achieved both the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol-defined corticosteroid taper regimen

[b] Sustained complete remission is defined as having achieved absence of GCA signs and symptoms from Week 12 through Week 52, normalization of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52, normalization of hsCRP to < 1 mg/dL without elevation to ≥ 1 mg/dL (on 2 consecutive visits) from Week 12 through Week 52, and adherence to the protocol-defined corticosteroid taper regimen

[c] Complete remission is defined as having achieved absence of GCA signs and symptoms, normalization of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met), normalization of hsCRP to < 1 mg/dL, and adherence to the protocol-defined corticosteroid taper regimen

[d] GCA flare is defined as an event representing recurrence of GCA signs or symptoms or an ESR measurement > 30 mm/hr (attributable to GCA) and requiring an increase in corticosteroid dose, and is only considered after all of the 3 following criteria are met: absence of recurrence of GCA signs and symptoms, normalization of ESR, and no corticosteroid dose increase. Subjects who do not have an assessment that meets all 3 criteria are considered as having a GCA flare at baseline. Time to first GCA flare is calculated from the time when all three criteria above are met. Subjects who meet all 3 criteria above but never experience GCA flare are censored at the last assessment

[e] p≤0.01

[f] p≤0.001

[g] Hazard ratio

[h] Odds ratio

Cumulative corticosteroid dose

Among patients who completed 52 weeks of follow-up, the cumulative corticosteroid exposure at week 52 was significantly lower in patients treated with upadacitinib 15 mg and a 26-week corticosteroid taper compared to placebo and a 52-week corticosteroid taper (median 1615 mg vs 2882 mg, respectively). The comparison of cumulative corticosteroid dose between the upadacitinib arm and the placebo arm is affected by the different pre-specified regimens for steroid tapering in the upadacitinib arm versus the placebo arm.

Health-related outcomes

Fatigue was assessed using FACIT-Fatigue score. Patients treated with upadacitinib 15 mg and a 26-week corticosteroid taper experienced significantly greater improvement from baseline compared to placebo and a 52-week corticosteroid taper in FACIT-Fatigue score at week 52 (4.0, 95% CI: 1.33, 6.76).

Health-related quality of life was assessed using SF-36. Patients receiving upadacitinib 15 mg and a 26-week corticosteroid taper experienced significantly greater improvement from baseline compared to placebo and a 52-week corticosteroid taper in the Physical Component Summary score of SF-36 at week 52 (3.75, 95% CI: 1.39, 6.11).

Atopic dermatitis

The efficacy and safety of upadacitinib 15 mg and 30 mg once daily were assessed in three Phase 3 randomised, double-blind, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 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 ~~12~~13).

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.

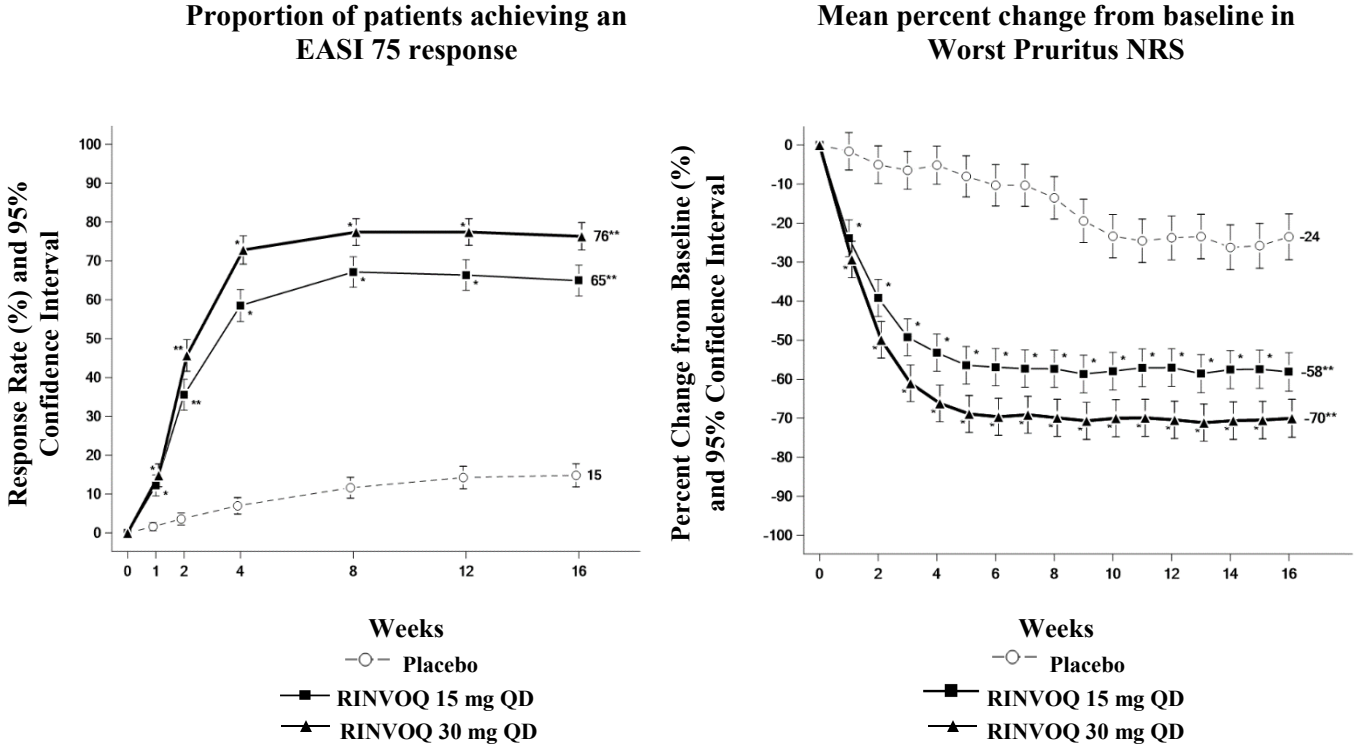
Table ~~12~~ 13 Efficacy results of upadacitinib

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



*: $p < 0.001$ 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 ~~13~~ 14 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)

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 $p < 0.001$

Ulcerative colitis

The efficacy and safety of upadacitinib was evaluated in three multicentre, double-blind, placebo-controlled Phase 3 clinical studies: two replicate induction studies, UC-1 (U-ACHIEVE Induction) and UC-2 (U-ACCOMPLISH), and a maintenance study UC-3 (U-ACHIEVE Maintenance). In addition, safety and efficacy of upadacitinib were assessed in a long-term extension study, UC-4 (U-ACTIVATE).

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

Induction studies (UC-1 and UC-2)

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

At baseline in UC-1 and UC-2, 39% and 37% of patients received corticosteroids, 1.1% and 0.6% of patients received methotrexate and 68% and 69% of patients received aminosalicylates. Concomitant use of thiopurine was not allowed during the studies. Patient disease activity was moderate (aMS ≥5, ≤7) in 61% and 60% of patients and severe (aMS >7) in 39% and 40% of patients.

The primary endpoint was clinical remission per aMS at week 8. Table ~~14~~ 15 shows the primary and key secondary endpoints including clinical response, mucosal healing, histologic-endoscopic mucosal healing and deep mucosal healing.

Table ~~14~~ 15 Proportion of patients meeting primary and key secondary efficacy endpoints at week 8 in the induction studies UC-1 and UC-2

	UC-1 (U-ACHIEVE)			UC-2 (U-ACCOMPLISH)		
Endpoint	**PBO N=154**	**UPA 45 mg N=319**	**Treatment Difference (95% CI)**	**PBO N=174**	**UPA 45 mg N=341**	**Treatment Difference (95% CI)**
Clinical remission[a]	4.8%	26.1%	21.6%* (15.8, 27.4)	4.1%	33.5%	29.0%* (23.2, 34.7)
Prior biologic failure[+]	0.4%	17.9%	17.5%	2.4%	29.6%	27.1%
Without prior biologic failure[+]	9.2%	35.2%	26.0%	5.9%	37.5%	31.6%
Clinical response[b]	27.3%	72.6%	46.3%* (38.4, 54.2)	25.4%	74.5%	49.4%* (41.7, 57.1)
Prior biologic failure[+]	12.8%	64.4%	51.6%	19.3%	69.4%	50.1%
Without prior biologic failure[+]	42.1%	81.8%	39.7%	31.8%	79.8%	48.0%
Mucosal healing[c]	7.4%	36.3%	29.3%* (22.6, 35.9)	8.3%	44.0%	35.1%* (28.6, 41.6)
Prior biologic failure[+]	1.7%	27.0%	25.3%	4.8%	37.1%	32.3%
Without prior biologic failure[+]	13.2%	46.8%	33.6%	12.0%	51.2%	39.2%
Histologic-endoscopic mucosal healing[d]	6.6%	30.1%	23.7%* (17.5, 30.0)	5.9%	36.7%	30.1%* (24.1, 36.2)
Prior biologic failure[+]	1.4%	22.7%	21.3%	4.6%	30.7%	26.1%
Without prior biologic failure[+]	11.8%	38.2%	26.4%	7.2%	42.9%	35.7%

Deep mucosal healing[e]	1.3%	10.7%	9.7%* (5.7, 13.7)	1.7%	13.5%	11.3%* (7.2, 15.3)
Prior biologic failure[+]	0	6.5%	6.5%	1.1%	9.2%	8.1%
Without prior biologic failure[+]	2.6%	15.4%	12.8%	2.4%	17.9%	15.5%

Abbreviations: PBO = placebo; UPA= upadacitinib; aMS = adapted Mayo Score, based on the Mayo Scoring system (excluding Physician's Global Assessment), which ranged from 0 to 9 and has three subscores that were each scored 0 (normal) to 3 (most severe): stool frequency subscore (SFS), rectal bleeding subscore (RBS) and a centrally-reviewed endoscopy subscore (ES).
[+]The number of "Prior biologic failure" patients in UC-1 and UC-2 are 78 and 89 in the placebo group, and 168 and 173 in the upadacitinib 45 mg group, respectively; the number of "Without prior biologic failure" patients in UC-1 and UC-2 are 76 and 85 in the placebo group, and 151 and 168 in the upadacitinib 45 mg group, respectively.
[*]p <0.001, adjusted treatment difference (95% CI)
[a] Per aMS: SFS≤ 1 and not greater than baseline, RBS = 0, ES ≤ 1 without friability
[b] Per aMS: decrease ≥ 2 points and ≥ 30% from baseline and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤ 1.
[c]ES ≤ 1 without friability
[d] ES ≤ 1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.)
[e] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Disease activity and symptoms

The partial adapted Mayo score (paMS) is composed of SFS and RBS. Symptomatic response per paMS is defined as a decrease of ≥1 point and ≥30% from baseline and a decrease in RBS ≥ 1 or an absolute RBS ≤1. Statistically significant improvement compared to placebo per paMS was seen as early as week 2 (UC-1: 60.1% vs 27.3% and UC-2: 63.3% vs 25.9%).

Extended induction

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

Maintenance study (UC-3)

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

The primary endpoint was clinical remission per aMS at week 52. Table ~~15~~ 16 shows the key secondary endpoints including maintenance of clinical remission, corticosteroid-free clinical remission, mucosal healing, histologic-endoscopic mucosal healing and deep mucosal healing.

Table ~~15~~ 16 Proportion of patients meeting primary and key secondary efficacy endpoints at week 52 in the maintenance study UC-3

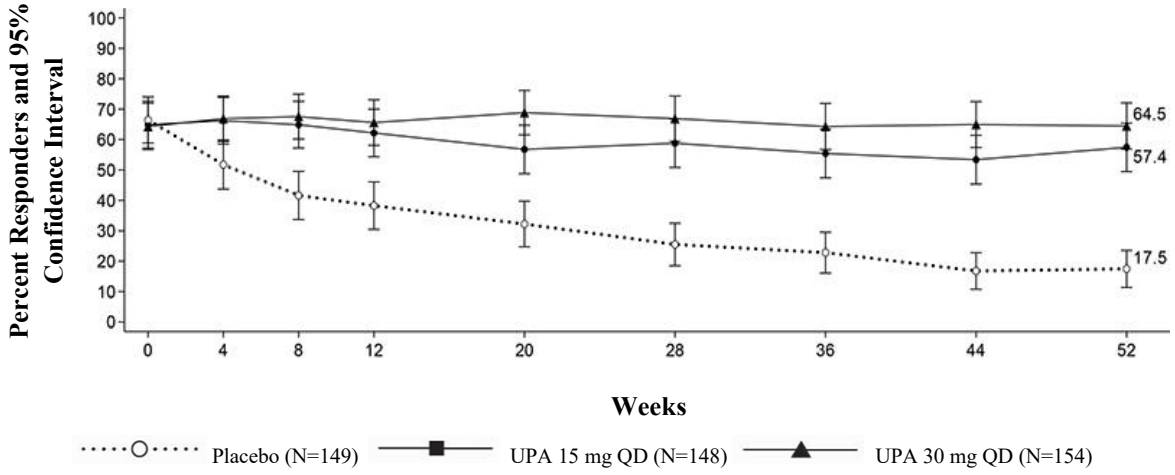
	PBO N=149	UPA 15 mg N=148	UPA 30 mg N=154	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Clinical remission[a]	12.1%	42.3%	51.7%	30.7%* (21.7, 39.8)	39.0%* (29.7, 48.2)
Prior biologic failure+	7.5%	40.5%	49.1%	33.0%	41.6%
Without prior biologic failure+	17.6%	43.9%	54.0%	26.3%	36.3%
Maintenance of clinical remission[b]	N = 54 22.2%	N = 47 59.2%	N = 58 69.7%	37.4%* (20.3, 54.6)	47.0%* (30.7, 63.3)
Prior biologic failure	N = 22 13.6%	N = 17 76.5%	N = 20 73.0%	62.8%	59.4%
Without prior biologic failure	N = 32 28.1%	N = 30 49.4%	N = 38 68.0%	21.3%	39.9%
Corticosteroid-free clinical remission[c]	N = 54 22.2%	N = 47 57.1%	N = 58 68.0%	35.4%* (18.2, 52.7)	45.1%* (28.7, 61.6)
Prior biologic failure	N = 22 13.6%	N = 17 70.6%	N = 20 73.0%	57.0%	59.4%
Without prior biologic failure	N = 32 28.1%	N = 30 49.4%	N = 38 65.4%	21.3%	37.2%
Mucosal healing[d]	14.5%	48.7%	61.6%	34.4%* (25.1, 43.7)	46.3%* (36.7, 55.8)
Prior biologic failure+	7.8%	43.3%	56.1%	35.5%	48.3%
Without prior biologic failure+	22.5%	53.6%	66.6%	31.1%	44.1%
Histologic-endoscopic mucosal healing[e]	11.9%	35.0%	49.8%	23.8%* (14.8, 32.8)	37.3%* (27.8, 46.8)
Prior biologic failure+	5.2%	32.9%	47.6%	27.7%	42.4%
Without prior biologic failure+	20.0%	36.9%	51.8%	16.9%	31.8%
Deep mucosal healing[f]	4.7%	17.6%	19.0%	13.0%* (6.0, 20.0)	13.6%* (6.6, 20.6)
Prior biologic failure+	2.5%	17.2%	16.1%	14.7%	13.6%
Without prior biologic failure+	7.5%	18.0%	21.6%	10.6%	14.2%

Abbreviations: PBO = placebo; UPA= upadacitinib; aMS = adapted Mayo Score, based on the Mayo Scoring system (excluding Physician's Global Assessment), which ranged from 0 to 9 and has three subscores that were each scored 0 (normal) to 3 (most severe): stool frequency subscore (SFS), rectal bleeding subscore (RBS) and a centrally-reviewed endoscopy subscore (ES).
[+]The number of "Prior biologic failure" patients are 81, 71, and 73 in the placebo, upadacitinib 15 mg, and 30 mg group, respectively. The number of "Without prior biologic failure" patients are 68, 77, and 81 in the placebo, upadacitinib 15 mg, and 30 mg group, respectively.
* p <0.001, adjusted treatment difference (95% CI)
[a] Per aMS: SFS≤ 1 and not greater than baseline, RBS = 0, ES ≤ 1 without friability
[b] Clinical remission per aMS at Week 52 among patients who achieved clinical remission at the end of induction treatment.
[c] Clinical remission per aMS at Week 52 and corticosteroid-free for ≥90 days immediately preceding Week 52 among patients who achieved clinical remission at the end of the induction treatment.
[d] ES ≤1 without friability
[e] ES ≤1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue).
[f] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue).

Disease symptoms

Symptomatic remission per paMS, defined as SFS ≤ 1 and RBS = 0, was achieved over time through week 52 in more patients treated with both upadacitinib 15 mg and 30 mg once daily compared with placebo (Figure 2).

Figure 2 Proportion of patients with symptomatic remission per partial adapted Mayo score over time in maintenance study UC-3



Endoscopic assessment

Endoscopic remission (normalisation of the endoscopic appearance of the mucosa) was defined as ES of 0. At week 8, a significantly greater proportion of patients treated with upadacitinib 45 mg once daily compared to placebo achieved endoscopic remission (UC-1: 13.7% vs 1.3%, UC-2: 18.2% vs 1.7%). In UC-3, a significantly greater proportion of patients treated with upadacitinib 15 mg and 30 mg once daily compared to placebo achieved endoscopic remission at week 52 (24.2% and 25.9% vs 5.6%). Maintenance of mucosal healing at week 52 (ES ≤1 without friability) was seen in a significantly greater proportion of patients treated with upadacitinib 15 mg and 30 mg once daily

compared to placebo (61.6% and 69.5% vs 19.2%) among patients who achieved mucosal healing at the end of induction.

Quality of life

Patients treated with upadacitinib demonstrated significantly greater and clinically meaningful improvement in health-related quality of life measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) total score compared to placebo. Improvements were seen in all 4 domain scores: systemic symptoms (including fatigue), social function, emotional function and bowel symptoms (including abdominal pain and bowel urgency). Changes in IBDQ total score at week 8 from baseline with upadacitinib 45 mg once daily compared to placebo were 55.3 and 21.7 in UC-1 and 52.2 and 21.1 in UC-2, respectively. Changes in IBDQ total score at week 52 from baseline were 49.2, 58.9 and 17.9 in patients treated with upadacitinib 15 mg, 30 mg once daily and placebo, respectively.

Long-term extension study (UC-4)

Patients who achieved clinical remission in UC-3 per aMS at 1 year were eligible to continue with the same dose in the extension study (UC-4). At the entry of UC-4, there were 96 and 146 patients in clinical remission and 49 and 82 patients in endoscopic remission with upadacitinib 15 mg and 30 mg, respectively. This population is partly, but not fully, overlapping with the population presented in the above table depicting proportion of patients meeting endpoints at week 52 in the maintenance study UC-3. Among patients who achieved remission in UC-3 per aMS at 1 year and had available 96 weeks data, 55/70 (78.6%) and 75/89 (84.3%) maintained clinical remission and 22/34 (64.7%) and 40/54 (74.1%) maintained endoscopic remission after 96 weeks of additional treatment with upadacitinib 15 mg and 30 mg, respectively.

In patients entering the extension study upon completion of UC-3 (1 year) and had available 96 weeks data, improvements in IBDQ total scores and in IBDQ domain scores were maintained through week 96 of UC-4.

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

Crohn's disease

The efficacy and safety of upadacitinib was evaluated in three multicenter, double-blind, placebo-controlled Phase 3 studies: two induction studies, CD-1 (U-EXCEED) and CD-2 (U-EXCEL), followed by a 52-week maintenance treatment and long-term extension study, CD-3 (U-ENDURE). The co-primary endpoints were clinical remission and endoscopic response at week 12 for CD-1 and CD-2, and at week 52 for CD-3.

Enrolled patients were 18 to 75 years of age with moderately to severely active Crohn's disease (CD), defined as an average daily very soft or liquid stool frequency (SF) ≥ 4 and/or average daily abdominal pain score (APS) ≥ 2, and a centrally-reviewed Simple Endoscopic Score for CD (SES-CD) of ≥ 6, or ≥ 4 for isolated ileal disease, excluding the narrowing component. Patients with symptomatic bowel strictures were excluded from CD studies.

Induction studies (CD-1 and CD-2)

In CD-1 and CD-2, 1021 patients (495 and 526 patients, respectively) were randomised to upadacitinib 45 mg once daily or placebo for 12 weeks with a 2:1 treatment allocation ratio.

In CD-1, all patients had inadequate response or were intolerant to treatment with one or more biologic therapies (prior biologic failure). Of these patients, 61% (301/495) had inadequate response or were intolerant to two or more biologic therapies.

In CD-2, 45% (239/526) patients had an inadequate response or were intolerant to treatment with one or more biologic therapies (prior biologic failure), and 55% (287/526) had an inadequate response or were intolerant to treatment with conventional therapies but not to biologic therapy (without prior biologic failure).

At baseline in CD-1 and CD-2, 34% and 36% of patients received corticosteroids, 7% and 3% of patients received immunomodulators, and 15% and 25% of patients received aminosalicylates.

In both studies, patients receiving corticosteroids at baseline initiated a corticosteroid taper regimen starting at week 4.

Both studies included a 12-week extended treatment period with upadacitinib 30 mg once daily for patients who received upadacitinib 45 mg once daily and did not achieve clinical response per SF/APS (≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily APS and neither greater than baseline) at week 12.

Clinical disease activity and symptoms

In CD-1 and CD-2, a significantly greater proportion of patients treated with upadacitinib 45 mg achieved the co-primary endpoint of clinical remission at week 12 compared to placebo (Table 17). Onset of efficacy was rapid and achieved as early as week 2 (Table 17).

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

Endoscopic assessment

In CD-1 and CD-2, a significantly greater proportion of patients treated with upadacitinib 45 mg achieved the co-primary endpoint of endoscopic response at week 12 compared to placebo (Table 17). In CD-1 and CD-2, a greater proportion of patients treated with upadacitinib 45 mg (14% and 19%, respectively) compared to placebo (0% and 5%, respectively) achieved SES-CD 0-2.

Table ~~16~~ 17 Proportion of patients meeting primary and additional efficacy endpoints in induction studies CD-1 and CD-2

Study	**CD-1 (U-EXCEED)**			**CD-2 (U-EXCEL)**		
Treatment Group	**PBO N=171**	**UPA 45 mg N=324**	**Treatment Difference (95% CI)**	**PBO N=176**	**UPA 45 mg N=350**	**Treatment Difference (95% CI)**
Co-Primary Endpoints at Week 12						
Clinical remission[a]	14%	40%	26% (19, 33)*	22%	51%	29% (21, 36)*
Prior biologic failure				N=78 14%	N=161 47%	33% (22, 44)
Without prior biologic failure				N=98 29%	N=189 54%	26% (14, 37)
Endoscopic response[b]	4%	35%	31% (25, 37)*	13%	46%	33% (26, 40)*
Prior biologic failure				N=78 9%	N=161 38%	29% (19, 39)
Without prior biologic failure				N=98 16%	N=189 52%	36% (25, 46)
Additional Endpoints at Week 12						

Clinical remission per CDAI[c]	21%	39%	18% (10, 26)*	29%	49%	21% (13, 29)*
Clinical response (CR-100)[d]	27%	51%	23% (14, 31)*	37%	57%	20% (11, 28)*
Corticosteroid-free clinical remission[a,e]	N=60 7%	N=108 37%	30% (19, 41)*	N=64 13%	N=126 44%	33% (22, 44)*
Endoscopic remission[f]	2%	19%	17% (12, 22)*	7%	29%	22% (16, 28)*
Mucosal healing[g]	N=171 0%	N= 322 17%	17% (13, 21)***	N=174 5%	N=349 25%	20% (14, 25)***
Early Onset Endpoints						
Clinical remission at Week 4[a]	9%	32%	23% (17, 30)*	15%	36%	21% (14, 28)*
CR-100 at Week 2[d]	12%	33%	21% (14, 28)*	20%	32%	12% (4, 19)**

Abbreviation: PBO = placebo, UPA = upadacitinib
* $p < 0.001$, adjusted treatment difference (95% CI)
** $p < 0.01$, adjusted treatment difference (95% CI)
*** nominal $p < 0.001$ UPA vs PBO comparison, adjusted treatment difference (95% CI)
[a] Average daily SF ≤ 2.8 and APS ≤ 1.0 and neither greater than baseline
[b] Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)
[c] CDAI < 150
[d] Decrease of at least 100 points in CDAI from baseline
[e] Discontinuation of steroid and achievement of clinical remission among patients on steroid at baseline
[f] SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable
[g] SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at baseline

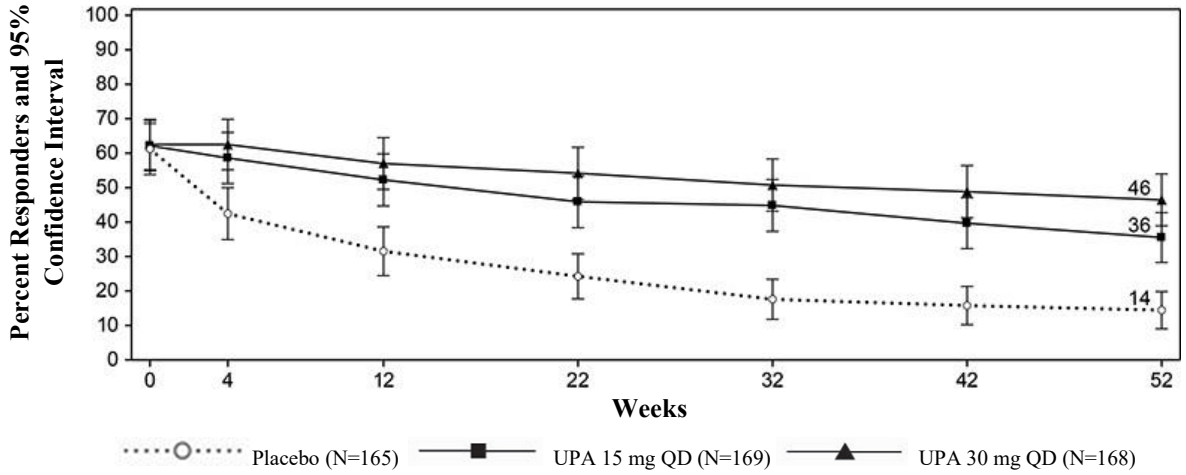
Maintenance study (CD-3)

The efficacy analysis for CD-3 evaluated 502 patients who achieved clinical response per SF/APS with the 12-week upadacitinib 45 mg once daily induction treatment. Patients were re-randomised to receive a maintenance regimen of either upadacitinib 15 mg or 30 mg once daily or placebo for 52 weeks.

Clinical disease activity and symptoms

A significantly greater proportion of patients treated with upadacitinib 15 mg and 30 mg achieved the co-primary endpoint of clinical remission at week 52 compared to placebo (Figure 3, Table 18).

Figure 3 Proportion of patients achieving clinical remission in maintenance study CD-3



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

Table ~~17~~ 18 Proportion of patients meeting primary and additional efficacy endpoints at week 52 in maintenance study CD-3

Treatment Group	PBO+ N=165	UPA 15 mg N=169	UPA 30 mg N=168	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Co-Primary Endpoints					
Clinical remission[a]	14%	36%	46%	22% (14, 30)*	32% (23, 40)*
Prior biologic failure	N=126 9%	N=124 32%	N=127 43%	24% (14, 33)	34% (24, 44)
Without prior biologic failure	N=39 33%	N=45 44%	N=41 59%	12% (-9, 33)	26% (5, 47)
Endoscopic response[b]	7%	28%	40%	21% (14, 28)*	34% (26, 41)*
Prior biologic failure	N=126 4%	N=124 23%	N=127 39%	19% (11, 27)	35% (26, 44)
Without prior biologic failure	N=39 18%	N=45 40%	N=41 44%	22% (3, 41)	26% (7, 45)
Additional Endpoints					
Clinical remission per CDAI[c]	15%	37%	48%	24% (15, 32)*	33% (24, 42)*
Clinical response (CR-100)[d]	15%	41%	51%	27% (18, 36)*	36% (28, 45)*
Corticosteroid-free clinical remission[a,e]	14%	35%	45%	21% (13, 30)*	30% (21, 39)*
Maintenance of clinical remission [a,f]	N=101 20%	N=105 50%	N=105 60%	32% (20, 44)*	40% (28, 52)*
Endoscopic remission[g]	5%	19%	29%	14% (8, 21)*	24% (16, 31)*

Mucosal healing[h]	N=164 4%	N=167 13%	N=168 24%	10% (4, 16)***	21% (14, 27)***
Deep remission [a,i]	4%	14%	23%	10% (4, 16)**	18% (11, 25)*

Abbreviation: PBO = placebo, UPA = upadacitinib
[+] The placebo group consisted of patients who achieved clinical response per SF/APS with upadacitinib 45 mg at the end of the induction study and were randomised to receive placebo at the start of maintenance therapy
[*] $p < 0.001$, adjusted treatment difference (95% CI)
[**] $p < 0.01$, adjusted treatment difference (95% CI)
[***] nominal $p < 0.001$ UPA vs PBO comparison, adjusted treatment difference (95% CI)
[a] Average daily SF ≤ 2.8 and APS ≤ 1.0 and neither greater than baseline
[b] Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)
[c] CDAI < 150
[d] Reduction of CDAI ≥ 100 points from baseline
[e] Corticosteroid-free for 90 days prior to week 52 and achievement of clinical remission. Among the subset of patients who were on corticosteroids at induction baseline, 38% (N=63) in upadacitinib 15 mg group, 38% (N=63) in upadacitinib 30 mg group, and 5% (N=61) in placebo were corticosteroid-free for 90 days prior to week 52 and in clinical remission
[f] Defined as achievement of clinical remission at Week 52 in patients who achieved clinical remission at the entry of the maintenance study
[g] SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore >1 in any individual variable
[h] SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at baseline
[i] Clinical remission and endoscopic remission

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

Endoscopic assessment

In CD-3, a significantly greater proportion of patients treated with upadacitinib 15 mg and 30 mg achieved the co-primary endpoint of endoscopic response at week 52 compared to placebo (Table 18). In addition to the endoscopic endpoints described in Table 18, a greater proportion of patients treated with upadacitinib 15 mg and 30 mg (11% and 21%, respectively) compared to placebo (3%) achieved SES-CD 0-2 at week 52. Corticosteroid-free endoscopic remission among patients on steroid at baseline was achieved in a greater proportion of patients treated with upadacitinib 15 mg and 30 mg (17% and 25%, respectively) compared to placebo (3%) at week 52.

Resolution of extra-intestinal manifestations

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

Rescue treatment

In CD-3, patients who demonstrated inadequate response or lost response during maintenance were eligible to receive rescue treatment with upadacitinib 30 mg. Of the patients who were randomised to

upadacitinib 15 mg group and received rescue treatment of upadacitinib 30 mg for at least 12 weeks, 84% (76/90) achieved clinical response per SF/APS and 48% (43/90) achieved clinical remission 12 weeks after initiating rescue.

Health-related quality of life outcomes

Patients treated with upadacitinib achieved greater improvement in health-related quality of life (HRQOL) measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) total score compared to placebo. Improvements were seen in all 4 domain scores: systemic symptoms (including fatigue) and bowel symptoms (including abdominal pain and bowel urgency), as well as social and emotional functioning. Changes from baseline in IBDQ total score at week 12 with upadacitinib 45 mg once daily compared to placebo were 46.0 and 21.6 in CD-1 and 46.3 and 24.4 in CD-2, respectively. Changes in IBDQ total score at week 52 from baseline were 59.3, 64.5 and 46.4 in patients treated with upadacitinib 15 mg, 30 mg once daily and placebo, respectively.

Paediatric population

Atopic dermatitis

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 ~~18~~ 19 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).

Polyarticular Juvenile Idiopathic Arthritis

The efficacy of RINVOQ 15 MG/RINVOQ LQ in paediatric patients with JIA with active polyarthritis is based on exposure-matched extrapolation of the established efficacy of RINVOQ in rheumatoid arthritis patients. Safety and efficacy of RINVOQ 15 MG/RINVOQ LQ were also assessed in a multicenter, open-label, single-arm study in 83 children (2 to < 18 years of age) with JIA with active polyarthritis (NCT03725007). The pJIA patient subtypes at study entry included rheumatoid factor negative polyarticular (68.7%), rheumatoid factor positive polyarticular (15.7%), extended oligoarticular (13.3%), and systemic JIA without systemic manifestations (2.4%). All patients received RINVOQ LQ or RINVOQ tablet dosages based on weight for up to 156 weeks. Patients treated with a stable dose of MTX were permitted to enter the study; changes in MTX dose were permitted during the study. Efficacy was assessed as supportive endpoints through Week 48. The efficacy was generally consistent with responses in patients with rheumatoid arthritis.

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.
Following the administration of the recommended paediatric dosage (see section 4.2) in pJIA and JPsA patients, the mean steady-state C_{max} is predicted to be 47.6 ng/mL and the mean steady-state AUC_{0-24} is predicted to be 342 ng·h/mL.

RINVOQ 15 MG and RINVOQ LQ are not bioequivalent; therefore, the two dosage forms are not interchangeable on a milligram-per-milligram basis.

Absorption

Following oral administration of upadacitinib prolonged-release formulation, upadacitinib is absorbed with a median T_{max} of 2 to 4 hours. Following oral administration of 6 mg RINVOQ LQ, upadacitinib is absorbed with a median T_{max} of 1 hour. Coadministration of upadacitinib prolonged-release formulation with a high-fat meal had no clinically relevant effect on upadacitinib exposures (increased AUC by 29% and C_{max} by 39% to 60%). Coadministration of RINVOQ LQ with food is not expected to have a clinically relevant effect on upadacitinib exposure. 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 after a single dose administration of 15 mg upadacitinib tablets 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 (see section 4.2).

Hepatic impairment

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC after a single dose administration of 15 mg upadacitinib tablets 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, axial spondyloarthritis, ulcerative colitis, and Crohn's disease (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. No clinical exposure data are available in adolescents < 40 kg.

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

In paediatric patients with JIA with active polyarthritis, upadacitinib clearance increased with increasing body weight. Age (over the range of 2 to < 18 years old) had no additional effect on upadacitinib pharmacokinetics after accounting for the effect of body weight. Upadacitinib plasma exposures in paediatric patients with pJIA and JPsA following the recommended paediatric dosage are predicted to be comparable to those observed in adult patients with rheumatoid arthritis and psoriatic arthritis, respectively.

Intrinsic factors

Age, sex, body weight, race, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure in adult patient populations. Upadacitinib pharmacokinetics are consistent between rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, giant cell arteritis, atopic dermatitis, ulcerative colitis, and Crohn's disease 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 tablets, 2 and 5 times the clinical dose of 30 mg tablets, and 1.7 and 4 times the clinical dose of 45 mg

tablets 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 17 and 34 times the maximum recommended human dose (MRHD) of 45 mg tablets 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 9 times the clinical exposure at the MRHD of 45 mg tablets (based on AUC).

In animal embryo-foetal development studies, upadacitinib was teratogenic in both rats and rabbits. Upadacitinib resulted in increases in skeletal malformations in rats at 1.6, 0.8, and 0.6 times the clinical exposure (AUC-based) at the 15, 30, and 45 mg tablets (MRHD) doses, respectively. In rabbits an increased incidence of cardiovascular malformations was observed at 15, 7.6 and 6 times the clinical exposure at the 15, 30, and 45 mg tablets doses (AUC-based), respectively.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

RINVOQ 15 MG, RINVOQ 30 MG prolonged-release tablets

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)

RINVOQ 45 MG prolonged-release tablets

Tablet contents:

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

Film coating:

Polyvinyl alcohol
Macrogol /Polyethylene Glycol
Titanium dioxide (E171)
Talc
Iron Oxide Yellow (E172)
Iron oxide red (E172)

RINVOQ LQ oral solution

Sucralose
Citric Acid, Anhydrous
Sodium Citrate, Dihydrate
Sodium Benzoate (E211)
Water, Purified

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

RINVOQ 15 MG, RINVOQ 30 MG prolonged-release tablets

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

RINVOQ 45 MG prolonged-release tablets

No special storage requirements.
Store in the original blister or bottle in order to protect from moisture. Keep the bottle tightly closed.

RINVOQ LQ oral solution

Store below 30°C. Can be refrigerated (2°C to 8°C). Do not freeze. Store the bottle upright in a carton, in a cool dark place.

Discard remaining oral solution 60 days after opening the bottle.

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.

RINVOQ 45 MG prolonged-release tablets

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

HDPE bottles with desiccant and polypropylene cap in carton containing 28 prolonged-release tablets.

Not all pack sizes may be marketed.

RINVOQ LQ oral solution

A 1 mg/mL oral solution in HDPE bottles with a child-resistant cap. Each bottle contains a labeled volume of 180 mL of clear, colorless to light yellow solution. The bottle is packaged in a carton with one press-in bottle adapter and one 10 mL oral dosing syringe.

6.6 Special precautions for disposal

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

7. MANUFACTURER

RINVOQ 15 MG /30 MG/45 MG TABLETS:
AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany

RINVOQ LQ ORAL SOLUTION:
AbbVie Inc., North Chicago, IL 60064, USA

8. LICENSE HOLDER

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

9. REGISTRATION NUMBER

RINVOQ 15 MG 164-29-36194

RINVOQ 30 MG 168-69-37036
RINOVQ 45 MG 172-42-37344
RINVOQ LQ 179-64-38152

Revised in ~~August~~ December 2025

<u>עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו – 1986</u>

התרופה משווקת על פי מרשם רופא בלבד

רינבוק® 15 מ"ג
רינבוק® 30 מ"ג
רינבוק® 45 מ"ג
רינבוק® אל.קיו

המרכיב הפעיל וכמותו:
כל טבליה לשחרור ממושך של רינבוק 15 מ"ג מכילה אופדסיטיניב (כהמיהדרט) 15 מ"ג
Upadacitinib (as hemihydrate) 15 mg
כל טבליה לשחרור ממושך של רינבוק 30 מ"ג מכילה אופדסיטיניב (כהמיהדרט) 30 מ"ג
Upadacitinib (as hemihydrate) 30 mg
כל טבליה לשחרור ממושך של רינבוק 45 מ"ג מכילה אופדסיטיניב (כהמיהדרט) 45 מ"ג
Upadacitinib (as hemihydrate) 45 mg
כל 1 מ"ל של תמיסה למתן דרך הפה של רינבוק אל.קיו מכילה אופדסיטיניב (כהמיהדרט) 1 מ"ג
Upadacitinib (as hemihydrate) 1 mg

חומרים בלתי פעילים ואלרגניים בתכשיר - ראה סעיף 6 "מידע נוסף" ו"מידע חשוב על חלק מהמרכיבים של התרופה" בסעיף 2 בעלון זה.

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך שאלות נוספות, פנה אל הרופא או אל הרוקח.
תרופה זו נרשמה לטיפול עבורך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מצבם הרפואי דומה.

בנוסף לעלון, לתכשיר רינבוק קיים כרטיס מידע בטיחותי למטופל. כרטיס זה מכיל מידע בטיחותי חשוב, שעליך לדעת, לפני התחלת הטיפול ובמהלך הטיפול ברינבוק ולפעול על פיו. יש לעיין בכרטיס מידע בטיחותי למטופל ובעלון לצרכן בטרם תחילת השימוש בתכשיר. יש לשמור את הכרטיס לעיון נוסף במידת הצורך.

1. <u>למה מיועדת התרופה?</u>

- רינבוק 15 מ"ג מיועד לטיפול בדלקת מפרקים שגרונית (Rheumatoid arthritis) פעילה בינונית עד חמורה במבוגרים, אשר חוו תגובה לא מספקת בטיפול בתרופה אנטי-ראומטית אחת או יותר מקבוצת DMARDs או שהטיפול היה בלתי נסבל עבורם. ניתן להשתמש ברינבוק כטיפול יחיד או בשילוב עם מתוטרקסאט (methotrexate).

- רינבוק 15 מ"ג מיועד לטיפול בדלקת מפרקים ספחתית (Psoriatic arthritis) פעילה במבוגרים, אשר חוו תגובה לא מספקת בטיפול בתרופה אנטי ראומטית אחת או יותר מקבוצת DMARDs או שהטיפול היה בלתי נסבל עבורם. ניתן להשתמש ברינבוק כטיפול יחיד או בשילוב עם מתוטרקסאט (methotrexate).

- ספונדילוארתריטיס אקסיאלית (Axial spondyloarthritis)
  - רינבוק 15 מ"ג מיועד לטיפול בספונדילוארתריטיס אקסיאלית פעילה ללא עדויות רדיוגרפיות (Non-radiographic axial spondyloarthritis [nr-axSpA]) במבוגרים עם סימני דלקת אובייקטיבים, שבאו לידי ביטוי על ידי רמות מוגברות של חלבון מגיב C (C-reactive protein – CRP) ו/או בהדמיה בתהודה מגנטית (MRI), אשר חוו תגובה לא מספקת לתרופות מקבוצת נוגדי דלקת שאינם סטרואידים (NSAIDs).

- רינבוק 15 מ״ג מיועד לטיפול בדלקת חוליות מקשחת פעילה (Ankylosing spondylitis ; radiographic axial spondyloarthritis [AS]) במבוגרים, אשר חוו תגובה לא מספקת לטיפול מקובל.

- ~~o~~ רינבוק 15 מ״ג מיועד לטיפול בדלקת עורקים של הרקה (Giant cell arteritis) במבוגרים.

- רינבוק 15 מ״ג/רינבוק 30 מ״ג מיועד לטיפול בדלקת עור אטופית (Atopic dermatitis) בינונית עד חמורה במבוגרים ובמתבגרים בגילאי 12 ומעלה אשר מועמדים לטיפול סיסטמי.

- רינבוק 15 מ״ג/רינבוק 30 מ״ג/רינבוק 45 מ״ג מיועד לטיפול בקוליטיס כיבית (Ulcerative colitis) פעילה בינונית עד חמורה במבוגרים, אשר חוו תגובה לא מספקת, אובדן תגובה או אי-סבילות לטיפול קונבנציונלי או ביולוגי.

- רינבוק 15 מ״ג/רינבוק 30 מ״ג/רינבוק 45 מ״ג מיועד לטיפול במחלת קרוהן (Crohn's disease) פעילה בינונית עד חמורה במבוגרים, אשר חוו תגובה לא מספקת, אובדן תגובה או אי-סבילות לטיפול קונבנציונלי או ביולוגי.

- רינבוק 15 מ״ג/רינבוק אל.קיו מיועד לטיפול בדלקת מפרקים ספחתית פעילה של גיל הילדות (JPsA] Juvenile psoriatic arthritis) בילדים מגיל שנתיים ומעלה, אשר חוו תגובה לא מספקת, או אי-סבילות לאחד או יותר מחוסמי TNF.

  רינבוק 15 מ״ג/רינבוק אל.קיו לא מומלץ לשימוש בשילוב עם מעכבי JAK אחרים, תכשירים ביולוגיים מקבוצת DMARDs או תרופות פוטנטיות לדיכוי מערכת החיסון כגון אזאתיופרין וציקלוספורין.

- רינבוק 15 מ״ג/רינבוק אל.קיו מיועד לטיפול בדלקת מפרקים אידיופטית פוליארטיקולרית פעילה של גיל הילדות (pJIA] Polyarticular juvenile idiopathic arthritis]) בילדים מגיל שנתיים ומעלה, אשר חוו תגובה לא מספקת, או אי סבילות לאחד או יותר מחוסמי TNF.

  רינבוק 15 מ״ג/רינבוק אל.קיו לא מומלץ לשימוש בשילוב עם מעכבי JAK אחרים, תכשירים ביולוגיים מקבוצת DMARDs או תרופות פוטנטיות לדיכוי מערכת החיסון כגון אזאתיופרין וציקלוספורין.

קבוצה תרפויטית: מדכאי מערכת חיסון סלקטיביים, מעכבי ג׳אנוס קינאז.

רינבוק פועל על ידי הפחתת הפעילות של אנזים בגוף הנקרא ״ג׳אנוס קינאז״ אשר מוריד דלקת.

דלקת מפרקים שגרונית
רינבוק משמש לטיפול בדלקת מפרקים שגרונית במבוגרים. דלקת מפרקים שגרונית זוהי מחלה הגורמת למפרקים מודלקים. אם אתה סובל מדלקת מפרקים שגרונית פעילה בינונית עד חמורה, ייתכן שתחילה תקבל תרופות אחרות, אשר אחת מהן תהיה ככל הנראה מתוטרקסאט. אם תרופות אלו לא השפיעו באופן מספק, תקבל רינבוק עם או ללא מתוטרקסאט לטיפול בדלקת המפרקים השגרונית שלך.

רינבוק יכול לעזור בהפחתת כאב, נוקשות ונפיחות במפרקים שלך, להפחית עייפות, ויכול להאט את הנזק לעצם ולסחוס במפרקים שלך. השפעות אלו יכולות להקל על הפעילות היום-יומית הרגילה שלך ובכך לשפר את איכות חייך.

דלקת מפרקים ספחתית
רינבוק משמש לטיפול בדלקת מפרקים ספחתית במבוגרים. דלקת מפרקים ספחתית הינה מחלה הגורמת למפרקים מודלקים ולפסוריאזיס. אם אתה סובל מדלקת מפרקים ספחתית פעילה, ייתכן שתחילה תקבל תרופות אחרות. אם

תרופות אלו לא השפיעו באופן מספק, תקבל רינבוק עם או ללא מתוטרקסאט לטיפול בדלקת המפרקים הספחתית שלך.

רינבוק יכול לעזור בהפחתת כאב, נוקשות ונפיחות במפרקים שלך ומסביבם, כאב ונוקשות בעמוד השדרה, נגעים ספחתיים בעור ועייפות ויכול להאט את הנזק לעצם ולסחוס במפרקים שלך. השפעות אלו יכולות להקל על הפעילות היום-יומית הרגילה שלך ובכך לשפר את איכות חייך.

ספונדילוארתריטיס אקסיאלית (ספונדילוארתריטיס אקסיאלית ללא עדויות רדיוגרפיות ודלקת חוליות מקשחת)
רינבוק משמש לטיפול בספונדילוארתריטיס אקסיאלית במבוגרים. ספונדילוארתריטיס אקסיאלית היא מחלה הגורמת בעיקר לדלקת בעמוד השדרה. אם אתה סובל מספונדילוארתריטיס אקסיאלית פעילה, ייתכן שתחילה תקבל תרופות אחרות. אם תרופות אלו לא השפיעו באופן מספק, תקבל רינבוק לטיפול בספונדילוארתריטיס האקסיאלית שלך.

רינבוק יכול לעזור בהפחתת כאבי גב, נוקשות ודלקת בעמוד השדרה. השפעות אלו יכולות להקל על הפעילות היום-יומית שלך ובכך לשפר את איכות חייך.

דלקת עורקים של הרקה
רינבוק משמש לטיפול בדלקת עורקים של הרקה במבוגרים. דלקת עורקים של הרקה הינה מחלה שגורמת לדלקת בכלי הדם, המשפיעה בדרך כלל על העורקים הבינוניים והגדולים בראש, בצוואר ובזרועות.

רינבוק יכול לעזור בשליטה בסימנים ובתסמינים של דלקת עורקים של הרקה כולל כאב ראש, רגישות בקרקפת, כאבי לסת ועייפות. השפעות אלו יכולות להקל על הפעילות היום-יומית שלך ובכך לשפר את איכות חייך. דלקת עורקים של הרקה מטופלת לעיתים קרובות באמצעות תרופות הנקראות סטרואידים. הן בדרך כלל יעילות, אך עלולות להיות להן תופעות לוואי אם משתמשים בהן במינונים גבוהים או אם משתמשים בהן למשך זמן ארוך. הפחתת מינון הסטרואידים עלולה גם להוביל להתלקחות של דלקת העורקים של הרקה. הוספת רינבוק לטיפול משמעותה שניתן להשתמש בסטרואידים לזמן קצר יותר, תוך שליטה במחלה.

דלקת עור אטופית
רינבוק משמש לטיפול בדלקת עור אטופית בינונית עד חמורה במבוגרים ובמתבגרים בגילאי 12 ומעלה. רינבוק ניתן לשימוש עם תרופות למריחה על העור שניתנות לדלקת עור אטופית או כטיפול יחיד.

נטילת רינבוק יכולה לשפר את מצב העור, להפחית גרד והתלקחויות. רינבוק יכול לסייע בשיפור תסמינים של כאב, חרדה ודיכאון אשר יכולים להופיע בחולים עם דלקת עור אטופית. רינבוק יכול גם לסייע בשיפור הפרעות שינה ואיכות החיים הכוללת.

קוליטיס כיבית
קוליטיס כיבית זו מחלה דלקתית של המעי הגס. רינבוק משמש לטיפול במבוגרים הסובלים מקוליטיס כיבית אשר הגיבו בצורה לא מספקת או שטיפול קודם לא היה נסבל עבורם.

רינבוק יכול לעזור בהפחתת סימנים ותסמינים של המחלה הכוללים דימום צואתי, כאב בטני, דחיפות ותכיפות הליכה לשירותים. השפעות אלו יכולות לאפשר קיום שגרת חיים תקינה והקלה בתשישות.

מחלת קרוהן
מחלת קרוהן זו מחלה דלקתית העלולה לערב כל חלק במערכת העיכול, אך בדרך כלל משפיעה על המעי. רינבוק משמש לטיפול במבוגרים הסובלים ממחלת קרוהן אשר הגיבו בצורה לא מספקת או שטיפול קודם לא היה נסבל עבורם.

רינבוק יכול לעזור בהפחתת סימנים ותסמינים של המחלה הכוללים דחיפות ותכיפות הליכה לשירותים, כאב בטני ודלקת של רירית המעי שלך. השפעות אלו יכולות לאפשר קיום שגרת חיים תקינה והקלה בתשישות.

דלקת מפרקים ספחתית של גיל הילדות (JPsA)
רינבוק משמש לטיפול בילדים מגיל שנתיים ומעלה עם דלקת מפרקים ספחתית של גיל הילדות. דלקת מפרקים ספחתית של גיל הילדות הינה מחלה הגורמת למפרקים מודלקים ולפסוריאזיס.

רינבוק צפוי לסייע בהפחתת כאב, נוקשות ונפיחות במפרקים שלך ומסביבם, כאב ונוקשות בעמוד השדרה שלך, פריחה ספחתית בעור, עייפות, ולעזור להאט את הנזק לעצם ולסחוס במפרקים שלך. השפעות אלו יכולות לעזור לך לבצע פעילויות יום-יומיות רגילות ובכך לשפר את איכות החיים שלך בכל הנוגע לבריאותך.

דלקת מפרקים אידיופטית פוליארטיקולרית של גיל הילדות (pJIA)
רינבוק משמש לטיפול בילדים מגיל שנתיים ומעלה עם דלקת מפרקים אידיופטית פוליארטיקולרית פעילה של גיל הילדות. דלקת מפרקים אידיופטית פוליארטיקולרית פעילה של גיל הילדות הינה מחלה הגורמת למפרקים מודלקים.

רינבוק צפוי לסייע בהפחתת כאב, נוקשות ונפיחות במפרקים שלך, עייפות, ולעזור להאט את הנזק לעצם ולסחוס במפרקים שלך. השפעות אלו יכולות לעזור לך לבצע פעילויות יום-יומיות רגילות ובכך לשפר את איכות החיים שלך בכל הנוגע לבריאותך.

2. <u>לפני השימוש בתרופה</u>

אין להשתמש בתרופה אם:
- אתה רגיש (אלרגי) לאופדסיטיניב או לכל אחד מהמרכיבים הנוספים אשר מכילה התרופה (מפורטים בסעיף 6)
- יש לך זיהום חריף (כגון דלקת ריאות או זיהום עור חיידקי)
- יש לך שחפת פעילה (TB)
- יש לך בעיות כבד חמורות
- הינך בהריון (ראי סעיף "הריון, הנקה ופוריות" מטה)

אזהרות מיוחדות הנוגעות לשימוש בתרופה

לפני הטיפול ובמהלך הטיפול ברינבוק ספר לרופא אם:
- יש לך זיהום או אם אתה מפתח זיהומים לעיתים תכופות. ספר לרופא שלך אם אתה מפתח תסמינים כגון חום, פצעים, הרגשת עייפות גדולה יותר מהרגיל או בעיות דנטליות, מאחר שאלה יכולים להיות סימנים לזיהום. רינבוק יכול להפחית את יכולת הגוף להילחם בזיהומים ועלול להחמיר זיהום קיים או להגביר את הסיכון להתפתחות זיהום חדש. אם אתה סובל מסוכרת או בן 65 ומעלה, אתה עלול להיות בסיכון מוגבר להתפתחות זיהומים.
- סבלת משחפת או שהיית במגע קרוב עם מישהו חולה שחפת. הרופא שלך יבצע בדיקה לשחפת לפני התחלת הטיפול ברינבוק וייתכן שיחזור על הבדיקה בזמן הטיפול.
- סבלת מזיהום הרפס זוסטר (שלבקת חוגרת), כיוון שרינבוק יכול לאפשר לזיהום לחזור. ספר לרופא שלך אם יש לך פריחה כואבת על העור עם שלפוחיות, כיוון שאלו יכולים להיות סימנים לשלבקת חוגרת.
- הייתה לך אי פעם דלקת כבד (הפטיטיס) מסוג B או C.
- קיבלת לאחרונה או שאתה עתיד לקבל חיסון – זאת כיוון שחיסונים חיים אינם מומלצים בזמן השימוש ברינבוק.
- יש לך סרטן או סבלת מסרטן בעבר, אתה מעשן או עישנת בעבר, מאחר שהרופא ידון עימך אם רינבוק מתאים עבורך.
- סרטן עור שאינו מלנומה נצפה במטופלים הנוטלים רינבוק. הרופא עשוי להמליץ לך על בדיקות עור סדירות במהלך נטילת רינבוק. אם במהלך או לאחר הטיפול מתפתחים נגעי עור חדשים או אם המראה של נגעים

קיימים משתנה, ספר לרופא.

- יש לך, או היו לך בעיות לב, מאחר שהרופא ידון עימך אם רינבוק מתאים עבורך.
- הכבד שלך אינו מתפקד כמו שצריך.
- היו לך בעבר קרישי דם בווריד הרגליים (פקקת וריד עמוקים) או בריאות (תסחיף ריאתי) או שאתה בעל סיכון מוגבר לפתח קרישי דם מסוג זה (לדוגמה: אם עברת ניתוח נרחב לאחרונה, אם את משתמשת באמצעי מניעה הורמונליים/בטיפול הורמונלי חלופי, אם זוהתה הפרעה בקרישת דם אצלך או אצל בני משפחה קרובים). הרופא ידון עימך אם רינבוק מתאים עבורך.
ספר לרופא שלך, אם אתה מפתח קוצר נשימה פתאומי או קושי בנשימה, כאב בחזה או כאב בגב העליון, נפיחות ברגל או ביד, כאב ברגל, -רגישות, או אודם או שינוי צבע ברגל או ביד, כיוון שאלו יכולים להיות סימנים לקרישי דם בווריד.
- אתה חווה שינויים פתאומיים בראייה שלך. פנה מיד לקבלת ייעוץ רפואי אם יש לך תסמינים פתאומיים כמו ראייה מטושטשת, אובדן ראייה חלקי או מלא, כיוון שאלו עלולים להיות סימן לחסימת זרימת הדם בעיניים.
- יש לך בעיות בכליות.
- יש לך כאב בטן בלתי מוסבר, יש או הייתה לך דלקת סעיף (דיברטיקוליטיס, דלקת כואבת של כיסים קטנים בדופן המעי שלך) או כיבים בקיבה או במעי, או הינך נוטל תרופות נוגדות דלקת לא סטרואידיות.
- אתה רואה טבליה או חלקי טבליה בצואה שלך בצורה חוזרת ונשנית.

אם אתה חווה אחת מתופעות הלוואי החמורות הבאות, פנה מיד לרופא שלך:

- תסמינים כגון פריחה (סרפדת), קשיים בנשימה או נפיחות של השפתיים, הלשון או הגרון, ייתכן שאתה חווה תגובה אלרגית. חלק מהאנשים שנטלו רינבוק חוו תגובות אלרגיות חמורות. אם אתה חווה אחד מהתסמינים במהלך הטיפול עם רינבוק, הפסק ליטול רינבוק ופנה לקבלת עזרה רפואית דחופה באופן מיידי.
- כאבי בטן עזים, במיוחד אלו המלווים בחום, בחילות והקאות.

בדיקות ומעקב

תצטרך לבצע בדיקות דם לפני התחלת הטיפול ברינבוק או בזמן נטילת התרופה. זאת כדי לבדוק אם קיימת ספירת תאי דם אדומים נמוכה (אנמיה), ספירת תאי דם לבנים נמוכה (נויטרופניה או לימפופניה), רמת שומנים גבוהה בדם (כולסטרול) או רמות גבוהות של אנזימי כבד. הבדיקות הן כדי לוודא שהטיפול ברינבוק אינו גורם לבעיות.

קשישים

קיים שיעור גבוה יותר של זיהומים בקרב חולים בגילאי 65 ומעלה. ספר לרופא שלך ברגע שאתה מבחין בסימנים או בתסמינים של זיהום.

מטופלים בגילאי 65 ומעלה עלולים להיות בסיכון מוגבר לזיהומים, לבעיות לב כולל התקף לב ולסוגי סרטן מסוימים. הרופא ידון עימך אם רינבוק מתאים עבורך.

ילדים ומתבגרים

רינבוק טבליות לא מומלץ לשימוש בילדים מתחת לגיל 12 או במתבגרים השוקלים פחות מ-30 ק״ג הסובלים מדלקת עור אטופית, מכיוון שהוא לא נחקר בחולים אלו.
הבטיחות והיעילות של רינבוק אל.קיו בילדים עם דלקת עור אטופית לא נקבעו.
רינבוק טבליות לא מומלץ לשימוש בילדים ובמתבגרים מתחת לגיל 18 עם ספונדילוארתריטיס אקסיאלית (ספונדילוארתריטיס אקסיאלית ללא עדויות רדיוגרפיות ודלקת חוליות מקשחת), קוליטיס כיבית או מחלת קרוהן זאת מכיוון שהוא לא נחקר בקבוצת גיל זו.
הבטיחות והיעילות של רינבוק 15 מ״ג/רינבוק אל.קיו בילדים מתחת לגיל שנתיים עם דלקת מפרקים אידיופטית פוליארטיקולרית של גיל הילדות או דלקת מפרקים ספחתית של גיל הילדות לא נקבעו.

אינטראקציות/תגובות בין תרופתיות

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא

או לרוקח. זאת מכיוון שתרופות מסוימות יכולות להפחית את יעילות הטיפול ברינבוק או עלולות להגביר את הסיכון לתופעות לוואי.

- תרופות לטיפול בזיהומים פטרייתיים (כגון איטראקונאזול, פוסאקונאזול או ווריקונאזול)
- תרופות לטיפול בזיהומים חיידקיים (כגון קלריתרומיצין)
- תרופות לטיפול בתסמונת קושינג (כגון קטוקונאזול)
- תרופות לטיפול בשחפת (כגון ריפאמפיצין)
- תרופות לטיפול בפרכוסים או התקפים (כגון פניטואין)
- תרופות המשפיעות על מערכת החיסון שלך (כגון אזאתיופרין, 6-מרקפטופורין, ציקלוספורין וטאקרולימוס)
- תרופות העלולות להעלות את הסיכון להתנקבות (פרפורציה) במערכת העיכול או לדלקת סעיף (דיברטיקוליטיס) כמו תרופות נוגדות דלקת לא סטרואידיות (לרוב משמשות לטיפול בכאב ו/או מצבי דלקת של השרירים או המפרקים), ו/או אופיואידים (משמשים לטיפול בכאבים עזים), ו/או קורטיקוסטרואידים (לרוב משמשים לטיפול במצבי דלקת)
- תרופות לטיפול בסוכרת או אם יש לך סוכרת. הרופא שלך עשוי להחליט אם אתה זקוק לפחות מהתרופה נגד סוכרת בזמן נטילת אופדסיטיניב (upadacitinib)

אם אתה לוקח את אחת מהתרופות מהרשימה מעלה או שאינך בטוח, ספר לרופא או לרוקח שלך לפני נטילת רינבוק.

הריון, הנקה ופוריות

<u>הריון</u>
אין להשתמש ברינבוק בזמן הריון.

<u>הנקה</u>
אם את מניקה או מתכננת להניק, דברי עם הרופא שלך לפני לקיחת תרופה זו. אין להשתמש ברינבוק בזמן הנקה כיוון שלא ידוע אם תרופה זו עוברת לחלב אם. את והרופא שלך תחליטו אם תניקי או תשתמשי ברינבוק. אל תעשי את שניהם.

<u>מניעת הריון</u>
אם את אישה בגיל הפוריות, עלייך להשתמש באמצעי מניעה יעילים כדי להימנע מהריון בזמן נטילת רינבוק ולמשך 4 שבועות לפחות לאחר מנת רינבוק האחרונה שלך. אם הרית בפרק זמן זה, עלייך לפנות מיד לרופא שלך.

אם הילדה שלך קיבלה לראשונה את המחזור החודשי בזמן נטילת רינבוק, עליך לעדכן את הרופא.

נהיגה ושימוש במכונות
אין לנהוג או להשתמש במכונות אם אתה חווה סחרחורת או תחושת סחרור (ורטיגו) בעת נטילת רינבוק עד שהן חולפות.

מידע חשוב על חלק מהמרכיבים של התרופה

רינבוק אל.קיו מכיל נתרן בנזואט (סודיום בנזואט). התמיסה מכילה 0.3 מ״ג נתרן בנזואט בכל 1 מ״ל של תמיסה למתן דרך הפה.

רינבוק אל.קיו מכיל נתרן (סודיום). התמיסה מכילה פחות מ-1 מילימול (23 מ״ג) נתרן בכל מנה, ולכן נחשבת ׳נטולת נתרן׳.

3. <u>כיצד תשתמש בתרופה</u> ?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא. עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע

למינון ואופן הטיפול בתכשיר.

המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

דלקת מפרקים שגרונית, דלקת מפרקים ספחתית, ~~או~~ ספונדילוארתריטיס אקסיאלית (ספונדילוארתריטיס אקסיאלית ללא עדויות רדיוגרפיות ודלקת חוליות מקשחת) או דלקת עורקים של הרקה

המינון המקובל בדרך כלל הוא 15 מ״ג פעם אחת ביום.

דלקת עור אטופית

מבוגרים:

המינון המקובל בדרך כלל הוא 15 מ״ג או 30 מ״ג פעם אחת ביום, כפי שנרשם על ידי הרופא שלך. הרופא עשוי להחליט אם להעלות או להוריד את המינון שלך בהתאם לפעולת התרופה בגוף.
קשישים:

אם אתה בן 65 ומעלה, המינון המקובל בדרך כלל הוא 15 מ״ג פעם אחת ביום.

מתבגרים (גילאי 12-17) השוקלים לפחות 30 ק״ג:

המינון המקובל בדרך כלל הוא 15 מ״ג פעם אחת ביום.

קוליטיס כיבית

המינון המקובל בדרך כלל הוא 45 מ״ג פעם ביום למשך 8 שבועות. הרופא שלך עשוי להחליט להאריך את המינון ההתחלתי של 45 מ״ג למשך 8 שבועות נוספים (סה״כ 16 שבועות). לאחר מכן המינון המקובל בדרך כלל הוא 15 מ״ג או 30 מ״ג פעם ביום כטיפול ארוך-טווח. הרופא עשוי להחליט להעלות או להוריד את המינון בהתאם לאופן שבו אתה מגיב לתרופה.

קשישים:

אם אתה בן 65 ומעלה, המינון המקובל בדרך כלל הוא 15 מ״ג פעם ביום כטיפול ארוך-טווח.

הרופא עשוי להחליט להוריד את המינון אם יש לך בעיות בכליות, או שנרשמו לך תרופות מסוימות אחרות.

מחלת קרוהן

המינון המקובל בדרך כלל הוא 45 מ״ג פעם ביום למשך 12 שבועות. לאחר מכן המינון המקובל בדרך כלל הוא 15 מ״ג או 30 מ״ג פעם ביום כטיפול ארוך-טווח. הרופא עשוי להחליט להעלות או להוריד את המינון בהתאם לאופן שבו אתה מגיב לתרופה.

קשישים:
אם אתה בן 65 ומעלה, המינון המקובל בדרך כלל הוא 15 מ״ג פעם ביום כטיפול ארוך טווח.

הרופא עשוי להחליט להוריד את המינון אם יש לך בעיות בכליות, או שנרשמו לך תרופות מסוימות אחרות.

דלקת מפרקים ספחתית של גיל הילדות או דלקת מפרקים אידיופטית פוליארטיקולרית של גיל הילדות

המינון המקובל למטופלים מגיל שנתיים ומעלה מבוסס על משקל הגוף.

- משקל מטופל של 10 ק״ג עד פחות מ-20 ק״ג:

רינבוק אל.קיו 3 מ״ג (3 מ״ל של תמיסה למתן דרך הפה) פעמיים ביום.
רינבוק 15 מ״ג (טבליות) אינו מומלץ.

- משקל מטופל של 20 ק״ג עד פחות מ-30 ק״ג:

רינבוק אל.קיו 4 מ״ג (4 מ״ל של תמיסה למתן דרך הפה) פעמיים ביום.
רינבוק 15 מ״ג (טבליות) אינו מומלץ.

- משקל מטופל של 30 ק״ג ומעלה:

רינבוק אל.קיו 6 מ״ג (6 מ״ל של תמיסה למתן דרך הפה) פעמיים ביום.
רינבוק 15 מ״ג (טבליה אחת של 15 מ״ג) פעם אחת ביום.

אין לעבור על המנה המומלצת

צורת הנטילה

- יש לבלוע את טבליות רינבוק בשלמותן עם מים. אין לחצות, לכתוש, ללעוס או לשבור את הטבליה לפני הבליעה כיוון שזה יכול לשנות את כמות התרופה הנכנסת לגופך.
- כדי לעזור לך לזכור לקחת רינבוק, קח אותו כל יום באותו הזמן.
- קח את טבליות רינבוק פעם ביום.
- קח את תמיסת רינבוק אל.קיו פעמיים ביום.
- ניתן לקחת טבליות רינבוק/תמיסת רינבוק אל.קיו עם או ללא מזון.
- הימנע ממזון או משקאות המכילים אשכוליות בזמן שאתה נוטל (או מטופל ב) רינבוק שכן אלו עלולים להגדיל את הסיכוי להופעת תופעות לוואי, על ידי הגדלת כמות התרופה בגופך.
- תמיסת רינבוק אל.קיו אינה זהה לטבליות רינבוק. אין להחליף בין תמיסת רינבוק אל.קיו לטבליות רינבוק אלא אם השינוי בוצע על ידי הרופא שלך.

קרא את סעיף 7 'הוראות שימוש' בסוף עלון זה לפני מתן מנה של רינבוק אל.קיו.

אם נטלת בטעות מינון גבוה יותר עליך לפנות לרופא שלך. ייתכן שתחווה מספר תופעות לוואי המפורטות בסעיף 4. אם אתה או ילדך נטלתם מנת יתר או אם בטעות בלע ילד מן התרופה, פנה מיד לרופא או לחדר מיון של בית חולים והבא אריזת התרופה איתך.

אם שכחת ליטול את התרופה

- אם פספסת מנה אחת, קח אותה מיד כשנזכרת.
- אם שכחת את המנה שלך במשך יום שלם, דלג על המנה שהפסדת וקח את המנה המומלצת כרגיל ביום למחרת.
- אין לקחת מנה כפולה כדי לפצות על מנה שנשכחה.

יש להתמיד בטיפול כפי שהומלץ על ידי הרופא.

אם אתה מפסיק את נטילת התרופה
אל תפסיק לקחת רינבוק אלא אם הרופא שלך הורה לך להפסיק לקחת אותו.

אין ליטול תרופות בחושך! בדוק התווית והמנה <u>בכל פעם</u> שהינך נוטל תרופה. הרכב משקפיים אם הינך זקוק להם.

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה זו, היוועץ ברופא או ברוקח.

4. <u>תופעות לוואי</u>

כמו בכל תרופה, השימוש ברינבוק עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן שלא תסבול מאף אחת מהן.

תופעות לוואי חמורות
דבר עם הרופא שלך או פנה מיד לקבלת עזרה רפואית אם אתה חווה סימנים כלשהם של:

- זיהום כגון שלבקת חוגרת או פריחה כואבת על העור עם שלפוחיות (הרפס זוסטר) - תופעות לוואי שכיחות (common) - תופעות שמופיעות ב-1-10 משתמשים מתוך 100
- זיהום בריאות (דלקת ריאות), אשר יכול לגרום לקוצר נשימה, חום ושיעול עם ליחה - תופעות לוואי שכיחות (common) - תופעות שמופיעות ב-1-10 משתמשים מתוך 100
- זיהום בדם (ספסיס) - תופעות לוואי שאינן שכיחות (uncommon) - תופעות שמופיעות ב-1-10 משתמשים מתוך 1,000
- תגובה אלרגית (לחץ בחזה, צפצופים, נפיחות של השפתיים, הלשון או הגרון, סרפדת) - תופעות לוואי שאינן שכיחות (uncommon) - תופעות שמופיעות ב-1-10 משתמשים מתוך 1,000

תופעות לוואי אחרות
דבר עם הרופא שלך אם הבחנת באחת מתופעות הלוואי הבאות:
<u>**תופעות לוואי שכיחות מאוד (very common) -** תופעות שמופיעות ביותר ממשתמש אחד מעשרה</u>

- זיהומים בגרון ובאף
- אקנה

<u>**תופעות לוואי שכיחות (common) -** תופעות שמופיעות ב-1-10 משתמשים מתוך 100</u>

- סרטן עור שאינו מלנומה
- שיעול
- חום
- פצעי קור (הרפס סימפלקס)
- בחילה
- עלייה ברמת אנזים אשר נקרא קראטין קינאז, הנראית בבדיקות דם
- ספירת תאי דם לבנים נמוכה, הנראית בבדיקות דם
- עלייה ברמות כולסטרול (סוג של שומן בדם) כפי שנראה בבדיקות
- עלייה ברמות אנזימי הכבד, הנראית בבדיקות דם (סימן לבעיות כבד)
- עלייה במשקל
- דלקת (נפיחות) של זקיקי השיער
- שפעת
- אנמיה
- כאב בטן
- עייפות (תחושת עייפות בלתי רגילה וחולשה)
- כאב ראש <u>(כאב ראש הינו שכיח מאד בדלקת עורקים של הרקה)</u>
- סרפדת (אורטיקריה)
- זיהום בדרכי השתן
- פריחה
- תחושת סחרור (ורטיגו)

- סחרחורת
- זיהום בריאות (ברונכיטיס)
- נפיחות של כפות הרגליים והידיים (בצקת היקפית)

תופעות לוואי שאינן שכיחות (uncommon) - תופעות שמופיעות ב-1-10 משתמשים מתוך 1,000

- פטרת הפה (כתמים לבנים בפה)
- עלייה ברמות טריגליצרידים (סוג של שומן) בדם כפי שנראה בבדיקות
- דלקת הסעיף (דיברטיקוליטיס, התפתחות דלקת כואבת בכיסים קטנים שנוצרים בדופן המעי שלך)
- התנקבות במערכת העיכול (חור במעי)

תופעות לוואי נוספות אצל מתבגרים עם אטופיק דרמטיטיס

תופעות לוואי שכיחות (common) - תופעות שמופיעות ב-1-10 משתמשים מתוך 100

- יבלות (פפילומה של העור)

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה או כאשר אתה סובל מתופעת לוואי שלא צוינה בעלון, עליך להתייעץ עם הרופא.

דיווח תופעות לוואי

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או על ידי כניסה לקישור:

https://sideeffects.health.gov.il

5. איך לאחסן את התרופה?

- מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם וטווח ראייתם של ילדים ו/או תינוקות ועל ידי כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.
- אין להשתמש בתרופה אחרי תאריך התפוגה (exp. date) המופיע על גבי האריזה החיצונית והבליסטר. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.
- עבור רינבוק 15 מ"ג ורינבוק 30 מ"ג:
יש לאחסן בטמפרטורה עד 30°C.
- עבור רינבוק 45 מ"ג:
אין תנאי אחסון מיוחדים. מומלץ לשמור בטמפרטורת החדר.
- יש לאחסן בבליסטר המקורי כדי להגן מלחות.
- עבור רינבוק אל.קיו:
יש לאחסן מתחת ל-30°C. ניתן לשמור בקירור (2°C -8°C). אין להקפיא. יש לאחסן את הבקבוק במצב זקוף בתוך קרטון, במקום קריר וחשוך.
יש להשליך את שארית התמיסה 60 יום לאחר פתיחת הבקבוק.
- אין להשליך תרופות כלשהן דרך הביוב או האשפה הביתית. שאל את הרוקח שלך כיצד להשליך תרופות אשר אינך משתמש בהן יותר. אמצעים אלו יעזרו לשמור על הסביבה.

6. מידע נוסף

מה מכיל רינבוק

נוסף על המרכיב הפעיל התרופה מכילה גם:

רינבוק 15 מ"ג טבליות לשחרור ממושך

- ליבת הטבליה:

Microcrystalline cellulose, mannitol, hypromellose, tartaric acid (powdered), magnesium stearate, silica colloidal anhydrous/colloidal silicon dioxide

- ציפוי הפילם:

Polyvinyl alcohol, macrogol/polyethylene glycol, talc, titanium dioxide (E171), black iron oxide (E172)/ferrosoferric oxide, iron oxide red (E172)

<u>רינבוק 30 מ״ג טבליות לשחרור ממושך</u>

- ליבת הטבליה:

Microcrystalline cellulose, mannitol, hypromellose, tartaric acid (powdered), magnesium stearate, silica colloidal anhydrous/colloidal silicon dioxide

- ציפוי הפילם:

Polyvinyl alcohol, macrogol/polyethylene glycol, talc, titanium dioxide (E171), iron oxide red (E172)

<u>רינבוק 45 מ״ג טבליות לשחרור ממושך</u>

- ליבת הטבליה:

Microcrystalline cellulose, mannitol, hypromellose, tartaric acid (powdered), magnesium stearate, silica colloidal anhydrous/colloidal silicon dioxide

- ציפוי הפילם:

Polyvinyl alcohol, macrogol/polyethylene glycol, titanium dioxide (E171), talc, iron oxide yellow (E172), iron oxide red (E172)

<u>רינבוק אל.קיו תמיסה למתן דרך הפה</u>

Sucralose, citric acid anhydrous, sodium citrate dihydrate, sodium benzoate (E211), purified water

כיצד נראית התרופה ומה תוכן האריזה

<u>רינבוק 15 מ״ג טבליות לשחרור ממושך</u>

רינבוק 15 מ״ג טבליות לשחרור ממושך הינן סגולות, מוארכות, קמורות משני הצדדים, מודפסות על צד אחד עם 'a15'.

הטבליות מסופקות בבליסטרים באריזות המכילות 28 או 98 טבליות לשחרור ממושך ובמארז של 84 טבליות המכיל 3 קופסאות, כל אחת מכילה 28 טבליות לשחרור ממושך.

כל בליסטר המציג את ימי השבוע מכיל 7 טבליות.

<u>רינבוק 30 מ״ג טבליות לשחרור ממושך</u>

רינבוק 30 מ״ג טבליות לשחרור ממושך הינן אדומות, מוארכות, קמורות משני הצדדים, מודפסות על צד אחד עם 'a30'.

הטבליות מסופקות בבליסטרים באריזות המכילות 28 או 98 טבליות לשחרור ממושך.

כל בליסטר המציג את ימי השבוע מכיל 7 טבליות.

<u>רינבוק 45 מ״ג טבליות לשחרור ממושך</u>

רינבוק 45 מ״ג טבליות לשחרור ממושך הינן צהובות עד צהובות מנוקדות, מוארכות, קמורות משני הצדדים, מודפסות על צד אחד עם 'a45'.

הטבליות מסופקות בבליסטרים באריזות המכילות 28 טבליות לשחרור ממושך.

כל בליסטר המציג את ימי השבוע מכיל 7 טבליות.

<u>רינבוק אל.קיו תמיסה למתן דרך הפה</u>

רינבוק אל.קיו תמיסה למתן דרך הפה היא תמיסה שקופה, חסרת צבע עד צהובה בהירה.
התמיסה מסופקת בבקבוק שמכיל 180 מ״ל תמיסה באריזת קרטון. אריזת הקרטון מכילה בנוסף לבקבוק גם מזרק רב פעמי ומתאם.

ייתכן שלא כל גודלי האריזות משווקים.

- **בעל הרישום וכתובתו:** אבווי ביופארמה בע״מ, רח׳ החרש 4, הוד השרון, ישראל
- **שם היצרן וכתובתו:**
  - **רינבוק 15 מ״ג/ 30 מ״ג/ 45 מ״ג טבליות:**
    אבווי דויטשלנד ג׳י.אמ.בי.אייץ׳ אנד קו. קיי.ג׳י, קנולשטרסה, 67061, לודויגשפן, גרמניה
  - **רינבוק אל.קיו תמיסה לבליעה:**
    אבווי בע״מ, צפון שיקגו, IL 60064, ארה״ב
- נערך ~~באוקטובר~~ בדצמבר 2025
- **מספר רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות:**
  רינבוק 15 מ״ג 164-29-36194
  רינבוק 30 מ״ג 168-69-37036
  רינבוק 45 מ״ג 172-42-37344
  רינבוק אל.קיו 179-64-38152

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.

7. <u>הוראות שימוש</u>

הוראות שימוש אלה מכילות מידע על אופן ההכנה והמתן של רינבוק אל.קיו תמיסה למתן דרך הפה.
קרא את הוראות השימוש לפני שאתה נותן רינבוק אל.קיו לילדך, ובכל פעם שאתה מקבל בקבוק חדש.
ייתכן שיהיה מידע חדש. מידע זה אינו מחליף שיחה עם הרופא שלך על מצבו הרפואי של ילדך או הטיפול בו.

מידע חשוב שעליך לדעת לפני מתן רינבוק אל.קיו

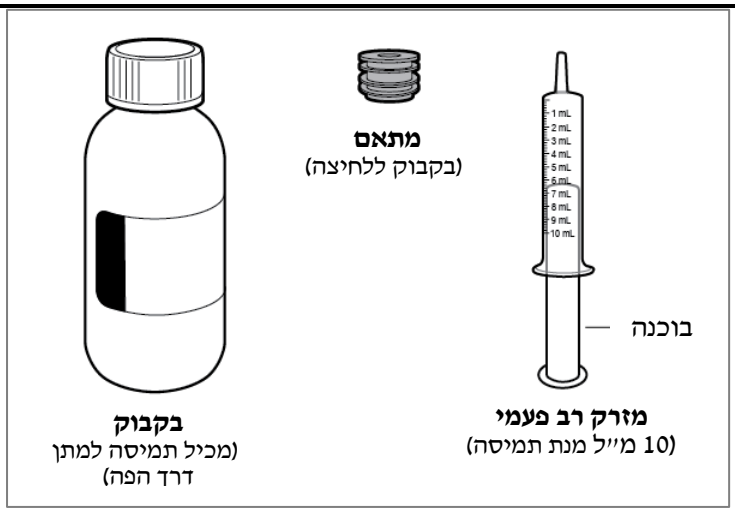
⚠ שמור את הבקבוק והציוד הרחק מהישג ידם וטווח ראייתם של ילדים.

⚠ השתמש אך ורק במזרק המצורף. **אל** תשתף את המזרק עם אנשים אחרים או תשתמש בו עם תרופות אחרות.

⚠ פנה לרופא שלך אם ילדך נטל יותר מדי מהתמיסה או לא קיבל את המנה המלאה.

- השתמש ברינבוק אל.קיו תוך 60 יום מפתיחת הבקבוק. כדי לעזור לך לזכור, רשום את התאריך בו פתחת את הבקבוק על הקרטון.
- **אל תפתח** בקבוק חדש של רינבוק אל.קיו עד שתסיים את הבקבוק הקודם. יש להשתמש במזרק חדש בעת פתיחת בקבוק חדש.
- תמיסה למתן דרך הפה רינבוק אל.קיו היא שקופה וחסרת צבע עד צהובה בהירה.
- שמור הוראות אלו ואת הקרטון שבו הגיעה תמיסת רינבוק אל.קיו והציוד לשימוש עתידי.

ציוד בכל קרטון



איור A

השלכת רינבוק אל.קיו

⚠ השלך (זרוק) את המזרק ואת הבקבוק לאחר שתסיים את השימוש בבקבוק או לאחר 60 יום מהפתיחה.

- שאל את הרוקח כיצד להשליך (לזרוק) תרופה שלא נעשה בה שימוש.
- שטוף את המזרק ולאחר מכן השלך אותו לפח האשפה הביתי.

הכנת רינבוק אל.קיו

1. בדוק את המינון שנרשם.

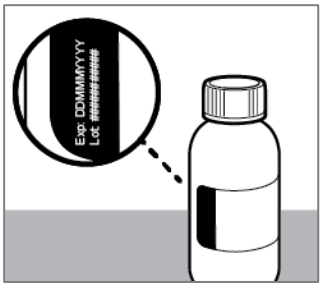
א. בדוק את המינון שנרשם לילדך במ״ל ומצא את סימון המ״ל על גבי המזרק.

ב. השתמש במזרק המצורף אך ורק כדי לתת את המינון שנרשם.

2. בדוק את תאריך התפוגה.

א. בדוק את הבקבוק וודא שתאריך התפוגה לא חלף (ראה **איור B**).

⚠ **אל** תשתמש ברינבוק אל.קיו לאחר שחלף תאריך התפוגה המודפס על גבי הקרטון והבקבוק אחרי הכיתוב "EXP".



איור B

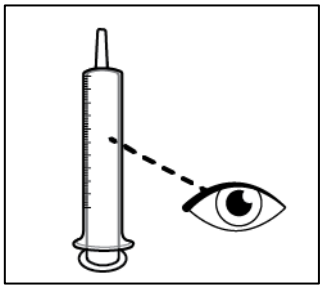
3. בדוק את הציוד.

א. בדוק את הציוד וודא שאינו פגום (ראה **איור C**).

ב. **השתמש במזרק רק אם הוא נקי ויבש.**

ג. וודא שהבוכנה משוכה עד קצה המזרק.

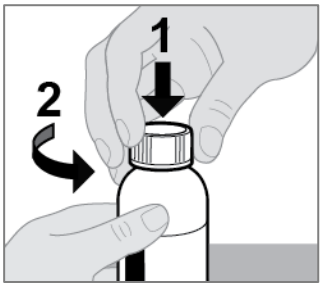
⚠ **אל** תשתמש בציוד אם הוא רטוב, פגום, או נראה שנפתח או נפגעה שלמותו.



איור C

4. פתח את הבקבוק.

א. לחץ כלפי מטה וסובב את המכסה כדי להסירו מהבקבוק (ראה **איור D**). **אל** תזרוק את המכסה.



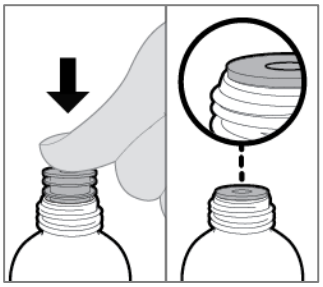
איור D

5. הכנס את המתאם (בפעם הראשונה בלבד).

א. תוך כדי אחיזת הבקבוק בחוזקה, דחוף את המתאם בעזרת האגודל שלך עד לקצה שפת הבקבוק (ראה **איור E**).

הערה: ייתכן שתצטרך להפעיל לחץ על המתאם.

⚠ **אל** תסיר את המתאם לאחר הכנסתו.



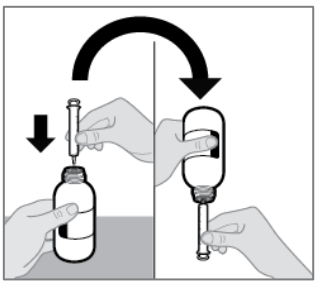
איור E

מדידת המנה

6. הכנס את המזרק לתוך הבקבוק ולאחר מכן הפוך את הבקבוק.

א. הכנס את קצה המזרק לתוך המתאם.

ב. כאשר המזרק מחובר לבקבוק, הפוך את הבקבוק (ראה **איור F**).



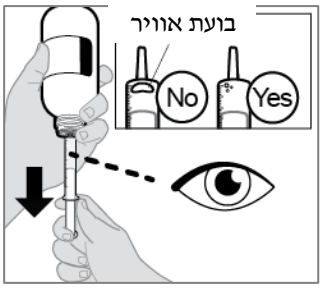
איור F

7. שאב את התמיסה לתוך המזרק.

א. משוך את הובכנה באיטיות כלפי מטה (ראה **איור G**).

ב. בדוק אם יש בועות אוויר במזרק.

הערה: ייתכן שתרגיש לחץ בעת משיכת הבוכנה.



איור G

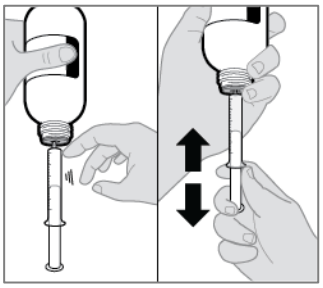
8. הסר בועות אוויר גדולות (ראה איור H).

א. תוך כדי אחיזת הבקבוק, הקש על צידי המזרק כדי לשלוח בועות אוויר גדולות לקצה.

ב. כאשר המזרק מחובר לבקבוק, הזז את הבוכנה למעלה ולמטה כדי להחזיר בועות אוויר חזרה לבקבוק.

ג. חזור על **שלב 8** עד שכל בועות האוויר הגדולות ייעלמו.

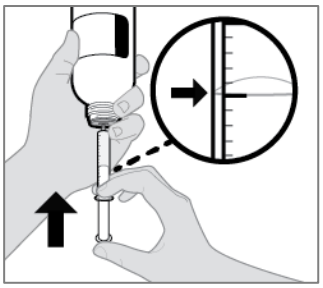
הערה: בועות אוויר קטנות הן נורמליות.



איור H

9. מדוד את המנה.

א. לאחר הסרת בועות אוויר גדולות, משוך את הבוכנה עד שתהיה בקו אחיד עם סימון המנה על גבי המזרק (ראה **איור I**).



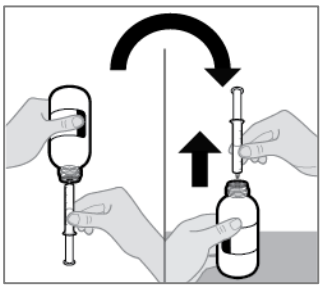
איור I

10. הפוך את הבקבוק בחזרה למצב עמידה, ואז הוצא את המזרק.

א. כאשר המזרק מחובר לבקבוק, הפוך את הבקבוק למצב עמידה.

ב. החזק במרכז המזרק והוצא אותו בזהירות מהבקבוק (ראה **איור J**).

⚠ **אל** תיגע בבוכנה כדי למנוע יציאה מקרית של תמיסה מהמזרק לפני שאתה מוכן לתת את התרופה.



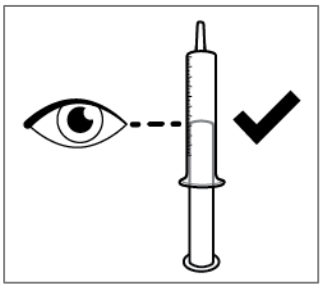
איור J

11. בדוק את המינון.

א. וודא שהמזרק מכיל את המינון הנכון של התמיסה למתן דרך הפה (ראה **איור K**).

ב. בדוק את המזרק לאיתור בועות אוויר גדולות.

ג. אם המינון אינו נכון או שאתה רואה בועות אוויר גדולות, חזור ל**שלב 6.**



איור K

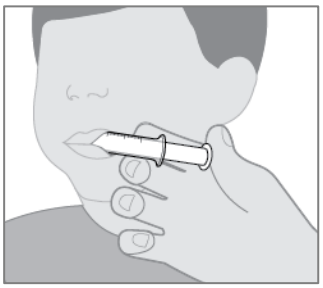
12. תן את התמיסה.

א. הנח את המזרק כנגד החלק הפנימי של לחיו של הילד.

ב. לחץ על הבוכנה כדי לתת את כל המנה לפיו של הילד (ראה **איור L**).

ג. תן לילד לשתות מים.

הערה: יש לתת את התמיסה תוך שעה ממילוי המזרק.



איור L

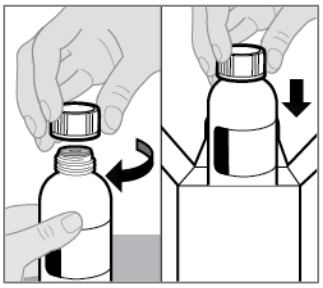
13. סגור ואחסן את הבקבוק.

א. כאשר המתאם עדיין מוכנס לבקבוק, הברג את המכסה בחזרה על הבקבוק כדי לאטום אותו (ראה **איור M**).

ב. אחסן את הבקבוק במצב זקוף בקרטון בין שימושים.

ג. אחסן את הבקבוק במצב זקוף בתוך קרטון מתחת ל-30°C במקום קריר וחשוך. ניתן לשמור בקירור (2°C -8°C). אין להקפיא.

ד. שמור את הבקבוק, הציוד, ואת כל התרופות הרחק מהישג ידם וטווח ראייתם של ילדים.



איור M

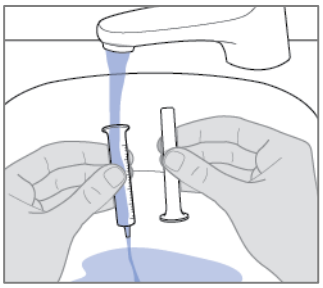
14. שטוף ואחסן את המזרק.

א. הוצא את הבוכנה מהמזרק ולאחר מכן שטוף את שני חלקיו במים (ראה **איור N**).

⚠ **אל** תשתמש בסבון ואל תכניס את המזרק למדיח כלים לניקויו.

ב. אפשר לחלקיו המופרדים של המזרק להתייבש באוויר על משטח נקי.

ג. אחסן את המזרק במקום נקי ויבש.



איור N

לאחר שסיימת את הבקבוק, עיין בסעיף "השלכת רינבוק אל.קיו".