*Date:* 20 January 2022
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*
## Extension of therapeutic indication

# Rinvoq

**International non-proprietary name:** upadacitinib as upadacitinib hemihydrate

**Pharmaceutical form:** prolonged-release tablet

**Dosage strength:** 15 mg

**Route(s) of administration:** oral

**Marketing Authorisation Holder:** AbbVie AG

**Marketing Authorisation No.:** 67257

**Decision and Decision date:** extension of therapeutic indication approved on 26 November 2021

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.



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## About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

## About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.



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# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| AD | Atopic dermatitis |
| ADA | Anti-drug antibody |
| ADME | Absorption, Distribution, Metabolism, Elimination |
| AEs | Adverse events |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| AUC0-24h | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| Cmax | Maximum observed plasma/serum concentration of drug |
| CYP | Cytochrome P450 |
| EASI | Eczema area and severity index |
| ERA | Environmental Risk Assessment |
| GLP | Good Laboratory Practice |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International Nonproprietary Name |
| JAK | Janus kinase |
| LoQ | List of Questions |
| MAH | Marketing Authorisation Holder |
| Max | Maximum |
| Min | Minimum |
| N/A | Not applicable |
| NO(A)EL | No Observed (Adverse) Effect Level |
| PD | Pharmacodynamics |
| PIP | Paediatric Investigation Plan (EMA) |
| PK | Pharmacokinetics |
| PopPK | Population PK |
| PSP | Pediatric Study Plan (US-FDA) |
| PY | Patient-year |
| RMP | Risk Management Plan |
| SAEs | Serious adverse events |
| SCORAD | SCORing atopic dermatitis |
| SwissPAR | Swiss Public Assessment Report |
| TCS | Topical corticosteroids |
| TEAEs | treatment-emergent adverse events |
| TNF | Tumour necrosis factor |
| TPA | Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21) |
| UPA | Upadacitinib |
| vIGA-AD | validated IGA for atopic dermatitis |



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# 2 Background Information on the Procedure

## 2.1 Applicant's Request(s)

**Extension(s) of the therapeutic indication(s)**
The applicant requested to add or change the indication in accordance with Article 23 TPO.

## 2.2 Indication and Dosage

### 2.2.1 Requested Indication

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

### 2.2.2 Approved Indication

RINVOQ is indicated for the treatment of moderate to severe atopic dermatitis in adults when conventional topical drug therapy does not provide adequate disease control or cannot be used.

### 2.2.3 Requested Dosage

The recommended dose for atopic dermatitis is 15 mg once daily. RINVOQ can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas.
RINVOQ treatment should be discontinued in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

### 2.2.4 Approved Dosage

(see appendix)

## 2.3 Regulatory History (Milestones)

| | |
|---|---|
| Application | 19 October 2020 |
| Formal control completed | 23 October 2020 |
| List of Questions (LoQ) | 27 January 2021 |
| Answers to LoQ | 25 March 2021 |
| Predecision | 1 June 2021 |
| Answers to Predecision | 10 August 2021 |
| Labelling corrections | 12 October 2021 |
| Answers to Labelling corrections: | 20 October 2021 |
| Final Decision | 26 November 2021 |
| Decision | approval |



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## 3 Medical Context

Atopic dermatitis (AD) is common (affecting up to 20% of children and 8% of adults). It is defined in different ways and may not necessarily constitute a single disease entity. AD is probably a multifactorial condition in which barrier abnormalities of the skin and immunological factors play important roles. Atopic dermatitis is diagnosed on the basis of clinical criteria (primarily those proposed by Hanifin and Rajka). Various scores are commonly used to determine its severity, including SCORing atopic dermatitis (SCORAD) and eczema area and severity index (EASI).
Most cases involve mild forms that can be well controlled with simple measures and topical treatment. But stubborn forms that can require costly and, in some cases, potentially burdensome systemic treatments also exist. The relevant guidelines recommend staged treatments for these scenarios.
Systemic treatments currently authorised in Switzerland:
Dupilumab
Cyclosporine
Baricitinib

## 4 Nonclinical Aspects

The submitted nonclinical information is considered appropriate to conduct a risk assessment for Rinvoq (active pharmaceutical ingredient upadacitinib) for the treatment of atopic dermatitis in adolescents (from 12 years of age) and adults.
Additional nonclinical studies were not submitted, which is acceptable as the available data are considered relevant for the newly requested indication. The previously conducted juvenile animal studies cover the age range for children from 2 years of age and did not reveal new toxicities. Safety margins were similar for the paediatric and adult patient populations. The overall risk assessment does not change from the nonclinical point of view with regard to the newly requested dose of 30 mg since the margins were already low or non-existent for the 15 mg dose.
A risk for the environment is not expected from the extended use.
From the nonclinical standpoint, there are no objections to approval of the proposed extension of indication.



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# 5 Clinical and Clinical Pharmacology Aspects

## 5.1 Clinical Pharmacology

To investigate the pharmacokinetics (PK) in patients with atopic dermatitis (AD), upadacitinib (UPA) levels were determined in all studies with such patients at differing times after the start of treatment. Values similar to those in patients with rheumatoid arthritis were described in these studies, and the PK model did not need to be modified.

## 5.2 Dose Finding and Dose Recommendation

In a randomised, controlled, double-blind Phase 2 study, the following treatments were compared in parallel groups:
Period 1, 16 weeks:
Placebo (N=41)
UPA 7.5 mg 1x1 (N=42)
UPA 15 mg 1x1 (N=42)
UPA 30 mg 1x1 (N=42)
Period 2, blinded extension, 72 weeks: The original placebo arm was randomised with UPA 30 mg/placebo on a 1:1 basis. The three UPA arms were randomised 1:1 and continued treatment either as before or with placebo (blinded rescue to 30mg < eczema area and severity index (EASI) 50% on/after week 20).
The study investigated patients with moderate to severe atopic dermatitis aged 18-75 years who failed to respond adequately to topical treatment with corticosteroids or calcineurin inhibitors, or for whom such treatments are not recommended for medical reasons.
The primary endpoint was the mean percent change from baseline in EASI score at week 16; secondary endpoints included the proportion of EASI 75 responders. The study described a dose-dependent improvement for the primary endpoint.

*Summary of Primary Endpoint Results at Week 16*
**(LOCF;_ITT_1 Population)**

| Dose | Mean Percentage Improvement in EASI Score |
|---|---|
| Upadacitinib 30 mg QD (n = 42) | 74%*** |
| Upadacitinib 15 mg QD (n = 42) | 62%*** |
| Upadacitinib 7.5 mg QD (n = 42) | 39%* |
| Placebo (n = 39) | 23% |

EASI = Eczema Area and Severity Index; QD = once daily
*p < 0.05, ***p < 0.001

Consistent improvements were also shown for secondary endpoints and Period 2, and the results were compatible with dose-dependent efficacy.
Although a dose-dependent increase was described for the frequency of treatment-emergent adverse events (TEAEs), the differences from placebo were small, and no serious adverse events (SAEs) or fatalities were recorded in Period 1. On the other hand, two fatalities were described during Period 2 in the UPA 30 mg arm, although the exposure with this dose, at 130.5 patient years, was much greater than in the other arms (20.7 patient years for UPA 15 mg and 15.2 patient years for UPA 7.5 mg).
Nevertheless, the safety data submitted for the whole clinical development package did show that the risk of adverse reactions can increase in line with the dose. This includes a numerical increase in TEAE-related dropouts (which leaves open the possibility of selection bias for long-term data), as well as numerical increases in malignancies and fatalities.



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## 5.3 Efficacy

The clinical development of UPA for the newly requested use in AD includes similar comparisons, such as the AD development of dupilumab and baricitinib. The UPA studies enrolled patients, around half of whom had been treated previously with non-biologic immunomodulating systemic therapies, and patients with/without systemic treatment were analysed as subgroups. However, patients who failed to respond to cyclosporine were not investigated in a specific study.
Three studies with comparable designs, endpoints and patient populations were submitted:
UPA monotherapy: M16-045 and M18-891
UPA in addition to topical corticosteroids: M16-047
In double-blind, randomised 1:1:1 parallel group comparisons, placebo treatment was compared with UPA treatment at the doses of 15 and 30 mg over 16 weeks. The 16-week placebo-controlled period was followed by a blinded extension of the UPA treatments up to 136 weeks. During the extension, the placebo arm was randomised 1:1 for a UPA treatment at the doses of 15 and 30 mg.
In the UPA study involving combination with topical corticosteroids (TCS), moderate TCS were used initially and had to be switched to mild TCS when the disease was under control or, at the latest, after 3 weeks. Potent or very potent TCS were permitted as rescue therapy in all studies from the 4th week of treatment.
This study enrolled patients with moderate to severe AD aged 12 and older (EASI ≥ 16) who had failed to respond to a topical treatment with a corticosteroid (TCS), or patients who had failed to respond to, or were ineligible for, conventional systemic immunosuppression. A total of 1683 patients were randomised for the two monotherapy studies, compared to 901 patients for the study in combination with TCS.
Primary/co-primary endpoints were the proportions of patients with EASI 75 and validated IGA for AD 0 or 1 in week 16. In a predefined test hierarchy, additional endpoints commonly used for AD were investigated, supplemented in study M18-891 by SCORAD-related variables.
All studies described a significantly better course with UPA compared to placebo across all hierarchically controlled endpoints (see Information for healthcare professionals, Tables 5 and 6).

## 5.4 Safety

Exposure: During the submitted studies investigating the use of UPA in atopic dermatitis, a total of 2893 patients were exposed, including 1805 patients in placebo-controlled studies (excluding the Japanese study M17-377). The corresponding overall experience from Phase 3 studies was 955 patient-year (PY) for UPA 15 mg and 974.2 PY for UPA 30 mg.
The patients were predominantly young adults (aged 18 and over, average age: 34).
Adverse events: One fatality occurred in the 16-week studies. In these studies, slightly more adverse events (AEs) were described for UPA, in a dose-dependent manner, than for placebo. As regards severe AEs, SAEs or AEs leading to discontinuation of study drug, the studies did not describe any consistent numerical imbalances.
Two fatalities were recorded during the long-term extension period of the Phase II study (M16-048) in patients taking UPA 30 mg.
Comparison with previous use in rheumatoid arthritis:
In a comparison of the safety profiles for the investigated use in atopic dermatitis with the authorised use in rheumatoid arthritis, no concerning differences were described for the 15 mg dose. Novel AEs were predominantly mild and involved skin manifestations, gastrointestinal symptoms and headache.

## 5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

In the submitted clinical development package, dose-dependent positive differences for common efficacy endpoints compared to placebo are described for UPA in AD in the investigated population. This benefit is offset by increased infections, increased lipid and creatinine phosphokinase levels, and a number of theoretical risks of adverse effects that are either rare or detected only after prolonged



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treatment. In February and September 2021, the U.S. Food and Drug Administration (FDA) stated that a long-term post-marketing study with the janus kinase (JAK) inhibitor tofacitinib found an increased risk of cardiac problems and malignancies compared to tumour necrosis factor (TNF) inhibitors, and warned that other JAK inhibitors, including UPA, may pose similar risks based on the current data situation.
Overall, a positive benefit/risk profile has been shown for the treatment of atopic dermatitis patients with UPA 15 mg when all relevant precautions are taken into account in the following indication: "RINVOQ is indicated for the treatment of moderate to severe atopic dermatitis in adults when conventional topical drug therapy does not provide adequate disease control or cannot be used."
The recommended oral dose of RINVOQ is 15 mg once daily.
The treatment with RINVOQ should be discontinued if no evidence of therapeutic benefit is shown after 12 weeks of treatment.

## 5.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.



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## 6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.



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# 7 Appendix

## 7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Rinvoq, prolonged-release tablets was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.



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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

## RINVOQ®

### Composition

*Active substances*

Upadacitinib as upadacitinib hemihydrate

*Excipients*

Microcrystalline cellulose, hypromellose, mannitol (E421), tartaric acid, silica (colloidal anhydrous), magnesium stearate, polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), black iron oxide (E172), iron oxide red (E172).

### Pharmaceutical form and active substance quantity per unit

*RINVOQ 15 mg prolonged-release tablets*

Purple oblong biconvex prolonged-release tablets imprinted on one side with ‘a15’.
Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib.

### Indications/Uses

*Rheumatoid Arthritis*

RINVOQ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis, who had an inadequate response or are intolerant to a treatment with one or more conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD).
RINVOQ may be used in combination with methotrexate or other csDMARDs or as monotherapy in adult patients.

*Psoriatic Arthritis*

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

*Ankylosing Spondylitis*

RINVOQ is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).

*Atopic Dermatitis*

RINVOQ is indicated for the treatment of moderate to severe atopic dermatitis in adults when conventional topical drug therapy does not provide adequate disease control or cannot be used.

**Dosage/Administration**

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

*Rheumatoid Arthritis*

The recommended dose of RINVOQ is 15 mg once daily.

*Psoriatic Arthritis*

The recommended dose of RINVOQ is 15 mg once daily.

*Ankylosing Spondylitis*

The recommended dose of RINVOQ is 15 mg once daily.

*Atopic Dermatitis*

*Adults*
The recommended dose of RINVOQ is 15 mg once daily.

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

RINVOQ treatment should be discontinued in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

*Administration*

RINVOQ tablets should be taken orally with or without food. RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

*Dose initiation*

It is recommended that RINVOQ is not used in patients with an absolute lymphocyte count (ALC) less than 500 cells/$mm^3$, an absolute neutrophil count (ANC) less than 1000 cells/$mm^3$ or who have hemoglobin levels less than 8 g/dL.

*Dose interruption*

If a patient develops a serious infection, RINVOQ treatment should be interrupted until the infection is controlled (see «Warnings and Precautions»).

**Table 1: Recommended Dose Interruption for Laboratory Abnormalities**

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

*Immunosuppressive medicinal products*

Combination with other potent immunosuppressants such as azathioprine, cyclosporine, tacrolimus, and biologic DMARDs or other Janus kinase (JAK) inhibitors has not been evaluated in clinical studies and is not recommended.

*Special dosage instructions*

*Patients with impaired hepatic function*

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. RINVOQ is not recommended for use in patients with severe hepatic impairment (Child Pugh C) (see «Pharmacokinetics»).

*Patients with impaired renal function*

No dose adjustment is required in patients with mild, moderate or severe renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease (estimated glomerular filtration rate <15 ml/min/1.73 $m^2$).

*Elderly patients*

No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older. There was a higher rate of overall adverse events, including serious infections, in the elderly.

*Children and adolescents*

The long-term safety of RINVOQ in children and adolescents aged 0 to 18 years have not yet been shown.

*Missed dose*

If a dose of RINVOQ is missed, it should be taken as soon as possible. The subsequent dose should be taken at the regularly scheduled time.

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients (see section «Composition»).

**Warnings and precautions**

*Serious infections*

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis (see «Undesirable effects»). Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis and cryptococcosis were reported with RINVOQ.

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

- with chronic or recurrent infections
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses

  or

- with underlying conditions that may predispose them to infection.

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

*Tuberculosis*
Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. TB prophylaxis must be initiated prior to initiation of RINVOQ in patients with previously untreated latent TB. Consultation with a physician with expertise in the treatment of TB is recommended if it has to be decided whether an anti-TB therapy is appropriate for an individual patient. Monitor patients for the development of signs and symptoms of TB, including patients who were tested negative for latent TB infection prior to initiating therapy.

*Viral reactivation*
Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B, were reported in clinical studies (see «Undesirable effects»). The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.
Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical

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

*Vaccination*
No data are available on the response to vaccination with live vaccines in patients receiving RINVOQ. Based on the current data, it cannot be assessed to which extent RINVOQ inhibits the immune response to neo and/or booster antigens. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including varicella/herpes zoster vaccinations (see «Properties/Effects» for data on inactivated pneumococcal 13-valent conjugate vaccine and concomitant use with RINVOQ). Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. If a live vaccine is considered prior to RINVOQ therapy, the time interval between live vaccination and treatment with RINVOQ must comply with the current vaccination guidelines for immunomodulatory agents. In accordance with these guidelines, live herpes zoster vaccine should only be administered to patients with a known history of chickenpox or who are chickenpox zona positive. The vaccine should be administered 4 weeks before treatment with an active immunomodulatory agent such as RINVOQ.

*Malignancy*
Immunomodulatory medications may increase the risk of malignancies including lymphoma. The effect of RINVOQ treatment on malignancies is not known.
Malignancies were observed in clinical studies of RINVOQ (see «Undesirable effects»). Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing RINVOQ in patients who develop a malignancy.

*Non-Melanoma Skin Cancer (NMSC)*
NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

*Thromboembolic events*
Thromboembolic events (deep vein thrombosis, lung embolism and arterial thrombosis) with sometimes fatal outcome were observed under the treatment with JAK inhibitors including RINVOQ. If clinicial features of a thromboembolic event occur, patients should be evaluated promptly, followed by appropriate treatment.

*Embryo-Fetal Toxicity*

RINVOQ may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception (see “Pregnancy, lactation”).

*Gastrointestinal perforations*
Gastrointestinal perforations were rarely observed under the treatment with RINVOQ.

*Hematological abnormalities*
Neutropenia – Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC < 1000 cells/$mm^3$). There was no clear association between low neutrophil counts and the occurrence of serious infections.
Lymphopenia - ALCs < 500 cells/$mm^3$ were reported in RINVOQ clinical studies. There was no clear association between low lymphocyte counts and the occurrence of serious infections.
Anemia – Decreases in hemoglobin levels to < 8 g/dL were reported in RINVOQ clinical studies.
The majority of the above hematologic laboratory changes were transient and resolved with temporary treatment interruption.
Evaluate at baseline and thereafter according to routine patient management. Treatment should not be initiated or should be temporarily interrupted in patients who meet the criteria described in Table 1 (see «Dosage/Administration»).

*Lipids*
Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see Undesirable effects). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.
Patients should be monitored 12 weeks after initiation of treatment and thereafter according to the international clinical guidelines for hyperlipidemia.

*Hepatic Transaminase Elevations*
Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo.
Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.
If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

**Interactions**

*Potential for other medicinal products to affect the pharmacokinetics of upadacitinib*
Upadacitinib is metabolized in vitro by CYP3A with a minor contribution from CYP2D6.

*Strong CYP3A4 inhibitors*
Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole). RINVOQ 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. Consider alternatives to strong CYP3A4 inhibitor medications when used in the long-term.

*Strong CYP3A4 inducers*
Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ (see «Pharmacokinetics»).
The concomitant use of RINVOQ with strong CYP3A4 inducers is not recommended.

*Other interactions*

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

The effect of co-administered medicinal products on upadacitinib plasma exposures is provided in Table 2.

**Table 2. Drug Interactions: Change in Pharmacokinetics of Upadacitinib in the presence of Co-administered Drugs**

| | | | | Ratio (90% CI)[a] | | |
|---|---|---|---|---|---|---|
| **Co-administered Drug** | **Regimen of Co-administered Drug** | **Regimen of Upadacitinib** | **N** | **$C_{max}$** | **AUC** | **Clinical Impact** |
| Ketoconazole | 400 mg daily x 6 days | 3 mg single dose [b] | 11 | 1.70 (1.55-1.89) | 1.75 (1.62-1.88) | Use with caution if used chronically. |
| Rifampicin | 600 mg once daily x 9 days | 12 mg single dose [b] | 12 | 0.49 (0.44-0.55) | 0.39 (0.37-0.42) | May decrease efficacy Concomitant intake not recommended |

CI: Confidence interval

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

[b] Upadacitinib was administered as an immediate-release formulation.

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

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

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

| | | | | Ratio (90% CI)[a] | | |
|---|---|---|---|---|---|---|
| **Co-administered Drug** | **Regimen of Co-administered Drug** | **Regimen of Upadacitinib** | **N** | **$C_{max}$** | **AUC** | **Clinical Impact** |
| Midazolam | 5 mg single dose | 30* mg once daily x 10 days | 20 | 0.74 (0.68-0.80) | 0.74 (0.68-0.80) | No dose adjustment |
| Rosuvastatin | 5 mg single dose | 30* mg once daily x 10 days | 12 | 0.77 (0.63-0.94) | 0.67 (0.56-0.82) | No dose adjustment |
| Atorvastatin | 10 mg single dose | 30* mg once daily x 10 days | 24 | 0.88 (0.79-0.97) | 0.77 (0.70-0.85) | No dose adjustment |

CI: Confidence interval

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

* This dose is not recommended in Switzerland

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

**Pregnancy, lactation**

*Pregnancy*

There are limited data on the use of upadacitinib in pregnant women. Studies in animals have shown reproductive toxicity (see «Preclinical Data»). 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*.
RINVOQ must not be used during pregnancy unless clearly necessary. Females of reproductive potential should be advised that effective contraception should be used during treatment and for 4 weeks following the final dose of RINVOQ.
If a patient becomes pregnant while taking RINVOQ, the parents should be informed of the potential risk to the foetus.

*Lactation*

It is unknown whether upadacitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk.
A risk to newborns/infants is possible. RINVOQ should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue RINVOQ 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 «Preclinical Data»).

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

The effect of RINVOQ on the ability to drive or use machines has not been specifically investigated.

**Undesirable effects**

*Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis*

*Summary of the safety profile*

The most commonly reported adverse drug reactions (ADRs) occurring in ≥ 2% of patients treated with RINVOQ either as monotherapy or in combination with conventional synthetic DMARDs were upper respiratory tract infections, bronchitis, nausea, cough and blood creatine phosphokinase (CPK) increased.
*Rheumatoid Arthritis*
A total of 4443 patients with rheumatoid arthritis were treated with upadacitinib in clinical studies representing 5263 patient-years of exposure, of whom 2972 were exposed to RINVOQ for at least one year. In the Phase 3 studies, 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1607 were exposed for at least one year.
Three placebo-controlled studies were integrated (1035 patients on RINVOQ 15 mg once daily and 1042 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 12-14 weeks after treatment initiation.
*Psoriatic Arthritis*
A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical studies representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the Phase 3 studies, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

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

*Ankylosing Spondylitis*

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

*Summary of adverse reactions*

The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Infections and infestations*

*Very Common:* Upper respiratory tract infections (URTI)[a] (13.5 %)

*Common:* Bronchitis[b], Herpes zoster, Herpes simplex[c]

*Uncommon:* Pneumonia, Oral candidiasis

*Blood and lymphatic system disorders*

*Common:* Neutropenia

*Metabolism and nutrition disorders*

*Common:* Hypercholesterolemia

*Uncommon:* Hypertriglycemia

*Respiratory, thoracic and mediastinal disorders*

*Common:* Cough

*Gastrointestinal disorders*

*Common:* Nausea

*Skin and subcutaneous tissue disorders*

*Common:* Acne

*General disorders*

*Common:* Pyrexia

*Investigations*

*Common:* Blood creatine phosphokinase (CPK) increased, ALT increased, AST increased, weight increased

[a] Includes upper respiratory tract infection, acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection
[b] Includes bronchitis, bronchitis viral, bronchitis bacterial, and tracheobronchitis
[c] Includes herpes simplexand oral herpes

*Rheumatoid Arthritis*

*Specific Adverse Reactions*

*Infections*
In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg group was 27.4% compared to 20.9% in the placebo group. In MTX-controlled studies, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group The overall long-term rate of infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies (2630 patients) was 93.7 events per 100 patient-years.
In placebo-controlled clinical studies with background DMARDs, the frequency of serious infection over 12/14 weeks in the RINVOQ 15 mg group was 1.2% compared to 0.6% in the placebo group. In MTX-controlled studies, the frequency of serious infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 0.6% compared to 0.4% in the MTX group. The overall long-term rate of serious infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most frequently reported serious infections were pneumonia and cellulitis. The rate of serious infections remained stable with long term exposure.

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

*Opportunistic Infections (excluding tuberculosis)*
In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the RINVOQ 15 mg group was 0.5% compared to 0.3% in the placebo group. In MTX-controlled studies, there were no cases of opportunistic infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group and 0.2% in the MTX group. The overall long-term rate of

opportunistic infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.6 events per 100 patient-years.

*Malignancy*

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

*Gastrointestinal Perforations*

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

*Thrombosis*

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

*Hepatic transaminase elevations*

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

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

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

*Lipid elevations*

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

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

*Creatine phosphokinase (CPK)*

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

*Neutropenia*

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

*Lymphopenia*

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

*Anemia*

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

*Psoriatic Arthritis*
Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher incidence of acne and bronchitis was observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

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

*Atopic Dermatitis*

*Summary of the safety profile*

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

A total of 2898 patients with atopic dermatitis were treated with RINVOQ in clinical studies representing approximately 3255 patient-years of exposure, of whom 1920 were exposed for at least one year. In the three global Phase 3 studies, 1239 patients received at least 1 dose of RINVOQ 15 mg, of whom 791 were exposed for at least one year.
Four global placebo-controlled studies (one Phase 2 study and three Phase 3 studies) were integrated (899 patients on RINVOQ 15 mg once daily and 902 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 16 weeks after treatment initiation.

*Summary of adverse reactions*

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

*Infections and infestations*
*Very Common:* Upper respiratory tract infections (URTI)[a] (22.6% for 15 mg and 25.4% for 30 mg)

*Common:* Herpes simplex[b], Herpes zoster, Folliculitis, influenza
*Uncommon:* Pneumonia, Oral candidiasis

*Blood and lymphatic system disorders*
*Common:* Neutropenia, Anemia

*Metabolism and nutrition disorders*
*Uncommon:* Hypercholesterolemia, Hypertriglyceridemia

*Respiratory, thoracic and mediastinal disorders*
*Common:* Cough

*Gastrointestinal disorders*
*Common:* Nausea, Abdominal pain[c]

*General disorders*
*Common:* Pyrexia, Fatigue

*Investigations*
*Common:* Blood creatine phosphokinase (CPK) increased, Weight increased
*Uncommon:* ALT increased, AST increased

*Skin and subcutaneous tissue disorders*
*Very common:* Acne (9.6% for 15 mg and 15.1% for 30 mg)
*Common:* Urticaria

*Nervous system disorders*
*Common:* Headache

[a] Includes laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
[b] Includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes
[c] Includes abdominal pain, abdominal pain upper

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

*Specific Adverse Reactions*

*Infections*

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

In placebo-controlled clinical studies, the frequency of serious infection over 16 weeks in the RINVOQ 15 mg group were 0.8% compared to 0.6% in the placebo group. The long-term rate of serious infections for the RINVOQ 15 mg group was 2.3 events per 100 patient-years. The most frequently reported serious infection was pneumonia.

*Tuberculosis*

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

*Opportunistic Infections (excluding tuberculosis)*

In the placebo-controlled period of the clinical studies, all opportunistic infections (excluding TB and herpes zoster) reported in the global AD studies were eczema herpeticum and the frequency of eczema herpeticum over 16 weeks in the RINVOQ 15 mg group was 0.7% compared to 0.4% in the placebo group. The long-term rate of eczema herpeticum for the RINVOQ 15 mg group was 1.6 events per 100 patient-years.

The long-term rate of herpes zoster for the RINVOQ 15 mg group was 3.5 events per 100 patient-years. Most of the herpes zoster events involved a single dermatome and were non-serious.

*Malignancy*

In the placebo-controlled clinical studies, there were no cases of malignancies excluding NMSC over 16 weeks reported in the group treated with RINVOQ 15 mg, the approved dose in Switzerland, and the and the group treated with placebo. The long-term incidence rate of malignancies excluding NMSC for the RINVOQ 15 mg group was 0.1 per 100 patient years.

*Gastrointestinal Perforations*

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

*Thrombosis*

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

*Hepatic transaminase elevations*

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

*Lipid elevations*

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

- Mean LDL cholesterol increased by 0.21 mmol/L in the RINVOQ 15 mg group.
- Mean HDL cholesterol increased by 0.19 mmol/L in the RINVOQ 15 mg group.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 0.09 mmol/L in the RINVOQ 15 mg group. Small increases in LDL cholesterol were observed after week 16.

*Creatine phosphokinase elevations*

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

*Neutropenia*

In placebo-controlled studies, for up to 16 weeks, dose-related decreases in neutrophil counts, below 1000 cells/$mm^3$ in at least one measurement occurred in 0.4% and 0% of patients in the RINVOQ 15 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to

ANC <1000 cells/mm$^3$. The pattern and incidence of decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

*Lymphopenia*
In placebo-controlled studies, for up to 16 weeks, decreases in lymphocyte counts below 500 cells/mm$^3$ in at least one measurement occurred in 0.1% of patients in the RINVOQ 15 mg and placebo groups.

*Anemia*
In placebo-controlled studies, there were no hemoglobin decreases below 8 g/dL in at least one measurement in patients in the RINVOQ 15 mg and placebo groups.

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. Healthcare professionals are asked to report any suspected new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Please find more information under www.swissmedic.ch.

**Overdose**

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

**Properties/Effects**

*ATC code*

L04AA44

*Mechanism of action*

Janus Kinases (JAKs) are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, 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. Upadacitinib is a selective and reversible inhibitor of JAK1. Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 50–70-fold greater selectivity for JAK1 over JAK2 and >100-fold for JAK1 over JAK3.

*Pharmacodynamics*

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

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

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

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

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

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

under stable treatment with upadacitinib 15 mg (n=87) or 30 mg (n=24). 97% of patients (n=108) were on concomitant methotrexate. Vaccination resulted in 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with upadacitinib 15 mg and 30 mg, respectively having an at least 2-fold increase in antibody concentration compared to the pre-vaccination baseline for at least 6 of the individual pneumococcal antigens of the vaccine. The extent to which this vaccine response allows protection against infection is unclear.

*Clinical efficacy*

*Rheumatoid Arthritis*

The efficacy and safety of RINVOQ 15 mg once daily was assessed in five Phase 3 randomized, double-blind, multicenter 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. All studies included long term extensions for up to 5 years.

**Table 4. Clinical Trial Summary**

| Study Name | Population (n) | Treatment Arms | Key Outcome Measures |
|---|---|---|---|
| SELECT-EARLY | MTX-naive[a] (947) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• MTX<br><br>Monotherapy | Primary Endpoint:<br>• ACR50 at Week 12<br>Key Secondary Endpoints:<br>• Clinical Remission (DAS28-CRP <2.6) at Week 24<br>• Low Disease Activity (DAS28-CRP ≤3.2) at Week 12<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• Radiographic progression (ΔmTSS) at Week 24<br>• SF-36 PCS |
| SELECT-MONOTHERAPY | MTX-IR[b] (648) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• MTX<br><br>Monotherapy | Primary Endpoint:<br>• ACR20 at Week 14<br>Key Secondary Endpoints: |

| | | | |
|---|---|---|---|
| | | | • Low Disease Activity (DAS28-CRP ≤3.2) at Week 14<br>• Clinical Remission (DAS 28-CRP <2.6) at Week 14<br>• Δ Physical Function (HAQ-DI) at Week 14<br>• SF-36 PCS<br>• Morning stiffness |
| SELECT-NEXT | csDMARD-IR[c] (661) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• Placebo<br><br>On background csDMARDs | Primary Endpoint:<br>• ACR20 at Week 12<br>Key Secondary Endpoints:<br>• Low Disease Activity (DAS28-CRP ≤3.2) at Week 12<br>• Clinical Remission (DAS28-CRP <2.6) at Week 12<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• SF-36 PCS<br>• Morning stiffness<br>• FACIT-F |
| SELECT-COMPARE | MTX-IR[d] (1629) | • Upadacitinib 15 mg<br>• Placebo<br>• Adalimumab 40 mg<br><br>On background MTX | Primary Endpoint:<br>• ACR20 at Week 12<br>Key Secondary Endpoints:<br>• Clinical Remission (DAS28-CRP <2.6) at Week 12<br>• Low Disease Activity (DAS28-CRP ≤3.2) at Week 12<br>• ACR50 vs adalimumab at Week 12<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• Radiographic progression (ΔmTSS) at Week 26<br>• SF-36 PCS<br>• Morning stiffness<br>• FACIT-F |
| SELECT-BEYOND | bDMARD-IR[e] | • Upadacitinib 15 mg | Primary Endpoint: |

| | | | |
|---|---|---|---|
| | (499) | • Upadacitinib 30 mg<br>• Placebo<br><br>On background csDMARDs | • ACR20 at Week 12<br>Key Secondary Endpoint:<br>• Low Disease Activity (DAS28-CRP ≤3.2) at Week 12<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• SF-36 PCS |
| Abbreviations: ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement, bDMARD = biologic disease-modifying anti-rheumatic drug; CR = Clinical Response, CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints, mTSS = modified Total Sharp Score, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, HAQ-DI = Health Assessment Questionnaire Disability Index, IR = inadequate responder, MTX = methotrexate<br><br>[a] Patients were naïve to MTX or received no more than 3 weekly MTX doses<br>[b] Patients had inadequate response to MTX<br>[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<br>[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<br>[e] Patients who had an inadequate response or intolerance to at least one bDMARD | | | |

*Clinical Response*

*Remission and low disease activity*

In all studies, a higher proportion of patients treated with RINVOQ 15 mg achieved both low disease activity (DAS28 CRP ≤3.2) and clinical remission (DAS28 CRP <2.6) compared to placebo, MTX, or adalimumab (Table 5). Compared to adalimumab, higher responses were achieved as early as Week 8 and maintained through Week 48. Higher responses were also observed for other disease activity outcomes including CDAI ≤2.8, SDAI ≤3.3, and Boolean remission. Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX.

*ACR Response*

In all studies, more patients treated with RINVOQ 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 for at least 1 year.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in greater improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP, compared to placebo, MTX monotherapy or adalimumab (Table 6).

In SELECT-COMPARE, a higher proportion of patients treated with RINVOQ 15 mg achieved ACR20/50/70 at Weeks 12 through 48 compared to adalimumab (Table 6).

**Table 5. Response and Remission**

| Study | SELECT EARLY MTX-naive | | SELECT MONO MTX-IR | | SELECT NEXT csDMARD-IR | | SELECT COMPARE MTX-IR | | | SELECT BEYOND bDMARD-IR | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | MTX | UPA 15 mg | MTX | UPA 15 mg | PBO | UPA 15 mg | PBO | UPA 15 mg | ADA 40 mg | PBO | UPA 15 mg |
| N | 314 | 317 | 216 | 217 | 221 | 221 | 651 | 651 | 327 | 169 | 164 |
| Week | | | | | | | | | | | |
| **ACR20 (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 54 | 76[g] | 41 | 68[e] | 36 | 64[e] | 36 | 71[e,i] | 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[e] | 15 | 42[g] | 15 | 38[g] | 15 | 45[g,h] | 29 | 12 | 34[g] |
| 24[c]/26[d] | 33 | 60[g] | | | | | 21 | 54[g,i] | 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,i] | 13 | 7 | 12 |
| 24[c]/26[d] | 18 | 44[g] | | | | | 10 | 35[g,i] | 23 | | |
| 48 | 29 | 51[g] | | | | | | 36[i] | 23 | | |
| **LDA DAS28-CRP ≤ 3,2 (% of patients )** | | | | | | | | | | | |
| 12[a]/14[b] | 28 | 53[f] | 19 | 45[e] | 17 | 48[e] | 14 | 45[e,i] | 29 | 14 | 43[e] |
| 24[c]26[d] | 32 | 60[g] | | | | | 18 | 55[g,i] | 39 | | |
| 48 | 39 | 59[g] | | | | | | 50[i] | 35 | | |
| **CR DAS28-CRP < 2,6 (% of patients )** | | | | | | | | | | | |
| 12[a]/14[b] | 14 | 36[g] | 8 | 28[e] | 10 | 31[e] | 6 | 29[e,i] | 18 | 9 | 29[g] |
| 24[c]26[d] | 18 | 48[f] | | | | | 9 | 41[g,i] | 27 | | |
| 48 | 29 | 49[g] | | | | | | 38[i] | 28 | | |
| **SDAI ≤ 3,3 (% of patients )** | | | | | | | | | | | |
| 12[a]14[b] | 6 | 16[g] | 1 | 14[g] | 3 | 10[g] | 3 | 12[g,i] | 7 | 5 | 9 |
| 24[c]/26[d] | 9 | 28[g] | | | | | 5 | 24[g,i] | 14 | | |
| 48 | 16 | 32[g] | | | | | | 25[i] | 17 | | |
| **CDAI ≤ 2,8 (% of patients )** | | | | | | | | | | | |
| 12[a]/14[b] | 6 | 16[g] | 1 | 13[g] | 3 | 9[g] | 3 | 13[g,i] | 8 | 5 | 8 |
| 24[c]/26[d] | 11 | 28[g] | | | | | 6 | 23[g,i] | 14 | | |
| 48 | 17 | 32[g] | | | | | | 25[i] | 17 | | |

| Boolesche Remission (% of patients ) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12[a]/14[b] | 6 | 13[g] | 1 | 9[g] | 4 | 10[g] | 2 | 10[g,i] | 4 | 2 | 7[g] |
| 24[c]/26[d] | 7 | 24[g] | | | | | 4 | 18[g,i] | 10 | | |
| 48 | 13 | 28[g] | | | | | | 21[i] | 15 | | |

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; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; SDAI = Simple Disease Activity Index; UPA= upadacitinib

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

[b] SELECT-MONOTHERAPY

[c] SELECT-EARLY

[d] SELECT-COMPARE

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

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

[g] Upadacitinib vs placebo or MTX comparison (These comparisons are not controlled for multiplicity)

[h] p≤0.001upadacitinib vs adalimumab comparison

[i] Upadacitinib vs adalimumab comparison (These comparisons are not controlled for multiplicity)

**Table 6: Components of ACR Response (mean change from baseline)[a]**

| **Study** | **SELECT EARLY MTX-Naive** | | **SELECT MONO MTX-IR** | | **SELECT NEXT csDMARD-IR** | | **SELECT COMPARE MTX-IR** | | | **SELECT BEYOND bDMARD-IR** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | MTX | UPA 15 mg | MTX | UPA 15 mg | PBO | UPA 15 mg | PBO | UPA 15 mg | ADA 40 mg | PBO | UPA 15 mg |
| N | 314 | 317 | 216 | 217 | 221 | 221 | 651 | 651 | 327 | 169 | 164 |
| Week | | | | | | | | | | | |
| **Number of tender joints (0-68)** | | | | | | | | | | | |
| 12[b]/ 14[c] | -13 | -17[h] | -11 | -15[h] | -8 | -14[h] | -10 | -16[h,l] | -14 | -8 | -16[h] |
| 24[d]/ 26[e] | -16 | -19[h] | | | | | -9 | -18[h,l] | -15 | | |
| **Number of swollen joints (0-66)** | | | | | | | | | | | |
| 12[b]/ 14[c] | -10 | -12[h] | -8 | -11[h] | -6 | -9[h] | -7 | -11[h,l] | -10 | -6 | -11[h] |
| 24[d]/ 26[e] | -12 | -14[h] | | | | | -6 | -12[h,l] | -11 | | |
| **Pain[f]** | | | | | | | | | | | |
| 12[b]/ 14[c] | -25 | -36[h] | -14 | -26[h] | -10 | -30[h] | -15 | -32[h,j] | -25 | -10 | -26[h] |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 24[d]/ 26[e] | -28 | -40[h] | | | | | -19 | -37[h,l] | -32 | | |
| **Patient global assessment[f]** | | | | | | | | | | | |
| 12[b]/ 14[c] | -25 | -35[h] | -11 | -23[h] | -10 | -30[h] | -15 | -30[h,l] | -24 | -10 | -26[h] |
| 24[d]/ 26[e] | -28 | -39[h] | | | | | -18 | -36[h,l] | -30 | | |
| **Disability Index (HAQ-DI)[g]** | | | | | | | | | | | |
| 12[b]/ 14[c] | -0.5 | -0.8[i] | -0.3 | -0.7[i] | -0.3 | -0.6[i] | -0.3 | -0.6[i,k] | -0.5 | -0.2 | -0.4[i] |
| 24[d]/ 26[e] | -0.6 | -0.9[h] | | | | | -0.3 | -0.7[h,l] | -0.6 | | |
| **Physician global assessment[f]** | | | | | | | | | | | |
| 12[b]/ 14[c] | -35 | -46[h] | -26 | -40[h] | -23 | -38[h] | -25 | -39[h] | -36 | -26 | -39[h] |
| 24[d]/ 26[e] | -45 | -50[h] | | | | | -27 | -45[h,l] | -41 | | |
| **hsCRP (mg/L)** | | | | | | | | | | | |
| 12[b]/ 14[c] | -10.6 | -17.5[h] | -1.1 | -10.2[h] | -0.4 | -10.1[h] | -1.7 | -12.5[h,l] | -9.2 | -1.1 | -11.0[h] |
| 24[d]/ 26[e] | -11.6 | -18.4[h] | | | | | -1.5 | -13.5[h,l] | -10.3 | | |

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CRP = c-reactive protein; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA = upadacitinib

[a] Data shown are mean

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

[c] SELECT-MONOTHERAPY

[d] SELECT-EARLY

[e] SELECT-COMPARE

[f] Visual analog scale: 0 = best, 100 = worst

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

[h] Upadacitinib vs placebo or MTX comparison (These comparisons are not controlled for multiplicity)
[i] p≤0.001 upadacitinib vs placebo or MTX comparison
[j] p≤0.001 upadacitinib vs adalimumab comparison
[k] p≤0.01 upadacitinib vs adalimumab comparison
[l] Upadacitinib vs adalimumab comparison (These comparisons are not controlled for multiplicity)

*Radiographic response*

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

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at week 26 and 48 in SELECT-COMPARE and as monotherapy compared to MTX at week 24 in SELECT-EARLY (Table 7). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with RINVOQ 15 mg compared to placebo at week 26 and 48 (SELECT-COMPARE) and compared to MTX at week 24 (SELECT-EARLY).

**Table 7: Radiographic Changes**

| **Study** | **SELECT EARLY MTX-Naive** | | **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[e] | 0.1 |
| Week 48 | | | 1.7 | 0.3[e] | 0.4 |
| **Erosion Score, mean change from baseline** | | | | | |
| Week 24[b]/26[c] | 0.3 | 0.1[e] | 0.4 | 0[e] | 0 |
| Week 48 | | | 0.8 | 0.1[e] | 0.2 |
| **Joint Space Narrowing Score, mean change from baseline** | | | | | |
| Week 24[b]/26[c] | 0.3 | 0.1[g] | 0.6 | 0.2[e] | 0.1 |
| Week 48 | | | 0.8 | 0.2[e] | 0.2 |
| **Proportion of patients with no radiographic progression[d]** | | | | | |
| Week 24[b]/26[c] | 77.7 | 87.5[f] | 76.0 | 83.5[f] | 86.8 |

| | | | | | |
|---|---|---|---|---|---|
| Week 48 | | | 74.1 | 86.4[e] | 87.9 |

Abbreviations: ADA = adalimumab; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA= upadacitinib

[a] All placebo data at week 48 derived using linear extrapolation

[b] SELECT-EARLY

[c] SELECT-COMPARE

[d] No progression defined as mTSS change ≤0.

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

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

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

*Physical function response and health-related outcomes*

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

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

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

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

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

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

*Psoriatic Arthritis*

The efficacy and safety of RINVOQ 15 mg once daily was assessed in two Phase 3 randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis (Table 8). 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. In both studies, previous treatment with cDMARD could be continued unchanged. The studies included long-term extensions for up to 5 years (SELECT-PsA 1) and 3 years (SELECT-PsA 2).

**Table 8: Clinical Trial Summary**

| **Study Name** | **Population (n)** | **Treatment Arms** | **Key Outcome Measures** |
|---|---|---|---|
| SELECT-PsA 1 | Non-biologic DMARD-IR[a] (1705) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• Placebo<br>• Adalimumab 40 mg | Primary Endpoint:<br>• ACR20 at Week 12 |
| | | | Key Secondary Endpoints:<br>• MDA at Week 24<br>• Resolution of enthesitis (LEI=0) and dactylitis (LDI=0) at Week 24<br>• PASI75 at Week 16<br>• sIGA at Week 16<br>• SAPS at Week 16<br>• Radiographic progression (ΔmTSS) at Week 24<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• SF-36 PCS at Week 12<br>• FACIT-F at Week 12<br>• ACR20, pain, and Δ Physical Function (HAQ-DI) vs adalimumab at Week 12 |
| SELECT-PsA 2 | bDMARD-IR[b] (642) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• Placebo | Primary Endpoint:<br>• ACR20 at Week 12 |
| | | | Key Secondary Endpoints:<br>• MDA at Week 24<br>• PASI75 at Week 16<br>• sIGA at Week 16<br>• SAPS at Week 16<br>• Δ Physical Function (HAQ-DI) at Week 12 |

| | | | |
|---|---|---|---|
| | | | • SF-36 PCS at Week 12<br>• FACIT-F at Week 12 |

Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement; bDMARD = biologic disease-modifying anti-rheumatic drug; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue score; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; MDA = minimal disease activity; mTSS = modified Total Sharp Score; PASI = Psoriasis Area and Severity Index; SAPS = Self-Assessment of Psoriasis Symptoms; SF-36 PCS = Short Form (36) Health Survey (SF-36) Physical Component Summary; sIGA = static Investigator Global Assessment of psoriasis

[a] Patients who had an inadequate response or intolerance to at least one non-biologic DMARD

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

*Clinical response*

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved ACR20 response compared to placebo at Week 12 (Table 9, Figure 1). In SELECT-PsA 1, RINVOQ 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at Week 12. A higher proportion of patients treated with RINVOQ 15 mg achieved ACR50 and ACR70 responses at Week 12 compared to placebo. Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 2 for ACR20.

Treatment with RINVOQ 15 mg resulted in improvements in individual ACR components, including tender/painful and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP compared to placebo (Table 10). Treatment with RINVOQ 15 mg resulted in greater improvement in pain compared to adalimumab at week 24.

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

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

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

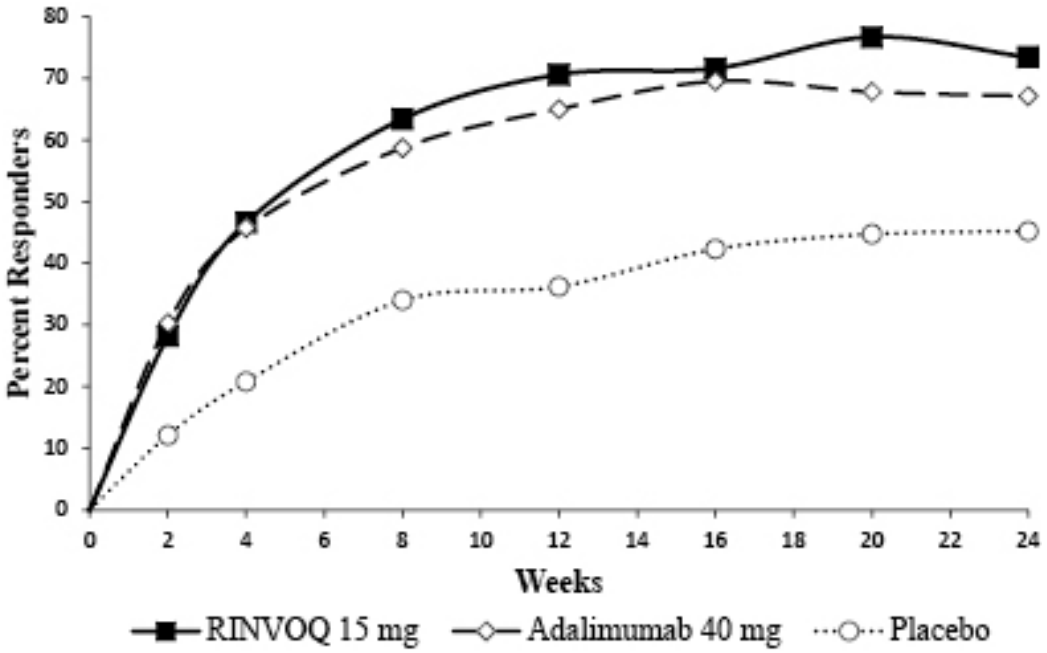



**Table 9: Clinical response**

| **Study** | **SELECT-PsA 1 non-biologic DMARD-IR** | | | **SELECT-PsA 2 bDMARD-IR** | |
|---|---|---|---|---|---|
| Treatment Group | PBO | UPA 15 mg | ADA 40 mg | PBO | UPA 15 mg |
| N | 423 | 429 | 429 | 212 | 211 |
| **ACR20 (% of patients)** | | | | | |
| Week 12 | 36 | 71[e] | 65 | 24 | 57[e] |
| Week 24 | 45 | 73[f,g] | 67 | 20 | 59[f] |
| Week 56 | | 74[g] | 69 | | 60 |
| **ACR50 (% of patients)** | | | | | |
| Week 12 | 13 | 38[f,g] | 38 | 5 | 32[f] |
| Week 24 | 19 | 52[f,g] | 44 | 9 | 38[f] |
| Week 56 | | 60[g] | 51 | | 41 |
| **ACR70 (% of patients)** | | | | | |
| Week 12 | 2 | 16[f,g] | 14 | 1 | 9[f] |
| Week 24 | 5 | 29[f,g] | 23 | 1 | 19[f] |
| Week 56 | | 41[g] | 31 | | 24 |
| **MDA (% of patients)** | | | | | |
| Week 12 | 6 | 25[f,g] | 25 | 4 | 17[f] |
| Week 24 | 12 | 37[e,g] | 33 | 3 | 25[e] |
| Week 56 | | 45[g] | 40 | | 29 |

| | | | | | |
|---|---|---|---|---|---|
| **Resolution of enthesitis (LEI=0; % of patients)[a]** | | | | | |
| Week 12 | 33 | 47[f, g] | 47 | 20 | 39[f] |
| Week 24 | 32 | 54[e,g] | 47 | 15 | 43[f] |
| Week 56 | | 59[g] | 54 | | 43 |
| **Resolution of dactylitis (LDI=0; % of patients)[b]** | | | | | |
| Week 12 | 42 | 74[f,g] | 72 | 36 | 64[f] |
| Week 24 | 40 | 77[g] | 74 | 28 | 58[f] |
| Week 56 | | 75[g] | 74 | | 51 |
| **PASI75 (% of patients)[c]** | | | | | |
| Week 16 | 21 | 63[e,g] | 53 | 16 | 52[e] |
| Week 24 | 27 | 64[f,g] | 59 | 19 | 54[f] |
| Week 56 | | 65[g] | 61 | | 52 |
| **PASI90 (% of patients)[c]** | | | | | |
| Week 16 | 12 | 38[f,g] | 39 | 8 | 35[f] |
| Week 24 | 17 | 42[f,g] | 45 | 7 | 36[f] |
| Week 56 | | 49[g] | 47 | | 41 |
| **PASI100 (% of patients)[c]** | | | | | |
| Week 16 | 7 | 24[f,g] | 20 | 6 | 25[f] |
| Week 24 | 10 | 27[f,g] | 28 | 5 | 22[f] |
| Week 56 | | 35[g] | 31 | | 27 |
| **sIGA 0/1 (% of patients)[d]** | | | | | |
| Week 16 | 11 | 42[e,g] | 39 | 9 | 37[e] |
| Week 24 | 12 | 45[f,g] | 41 | 10 | 33[f] |
| Week 56 | | 52[g] | 47 | | 33 |

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; MDA = minimal disease activity; MTX = methotrexate; PASI75 (or 90 or 100) = ≥75% (or ≥90% or 100%) improvement in Psoriasis Area and Severity Index; PBO = placebo; sIGA = static Physician Global Assessment; UPA= upadacitinib

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

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

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

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

[d] In patients with sIGA ≥ 2 at baseline (n=313, 322, and 330, respectively, for SELECT-PsA 1 and n=163 and 171, respectively, for SELECT-PsA 2)

[e] p≤0.001 upadacitinib vs placebo comparison

[f] Upadacitinib vs placebo comparisons were not controlled for multiplicity.

[g] Upadacitinib vs adalimumab comparisons were not controlled for multiplicity.

**Table 10: Components of ACR Response (mean change from baseline)**

| **Study** | **SELECT-PsA 1 non-biologic DMARD-IR** | | | **SELECT-PsA 2 bDMARD-IR** | |
|---|---|---|---|---|---|
| Treatment Group | PBO | UPA 15 mg | ADA 40 mg | PBO | UPA 15 mg |
| N | 423 | 429 | 429 | 212 | 211 |
| **Number of tender/painful joints (0-68)** | | | | | |
| Week 12 | -7.1 | -11.3[d,e] | -10.3 | -6.2 | -12.4[d] |
| Week 24 | -9.2 | -13.7[d,e] | -12.5 | -6.6 | -14.0[d] |
| **Number of swollen joints (0-66)** | | | | | |
| Week 12 | -5.3 | -7.9[d,e] | -7.6 | -4.8 | -7.1[d] |
| Week 24 | -6.3 | -9.0[d,e] | -8.6 | -5.6 | -8.3[d] |
| **Patient assessment of pain[a]** | | | | | |
| Week 12 | -0.9 | -2.3[d] | -2.3 | -0.5 | -1.9[d] |
| Week 24 | -1.4 | -3.0[d,e] | -2.6 | -0.7 | -2.2[d] |
| **Patient global assessment[a]** | | | | | |
| Week 12 | -1.2 | -2.7[d,e] | -2.6 | -0.6 | -2.3[d] |
| Week 24 | -1.6 | -3.4[d,e] | -2.9 | -0.8 | -2.6[d] |
| **Disability index (HAQ-DI)[b]** | | | | | |
| Week 12 | -0.14 | -0.42[c] | -0.34 | -0.10 | -0.30[c] |
| Week 24 | -0.19 | -0.51[d,e] | -0.39 | -0.08 | -0.33[d] |
| **Physician global assessment[a]** | | | | | |
| Week 12 | -2.1 | -3.6[d,e] | -3.4 | -1.4 | -3.1[d] |
| Week 24 | -2.8 | -4.3[d,e] | -4.1 | -1.8 | -3.8[d] |
| **hsCRP (mg/L)** | | | | | |
| Week 12 | -1.3 | -7.1[d,e] | -7.6 | 0.3 | -6.6[d] |

| | | | | | |
|---|---|---|---|---|---|
| Week 24 | -2.1 | -7.6[d,e] | -7.3 | -0.9 | -6.3[d] |

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; hsCRP = c-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; PBO = placebo; UPA = upadacitinib

[a] Numeric rating scale (NRS): 0 = best, 10 = worst

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

[c] p≤0.001 upadacitinib vs placebo comparison

[d] Upadacitinib vs placebo comparisons were not controlled for multiplicity.

[e] Upadacitinib vs adalimumab comparisons were not controlled for multiplicity.

In both studies, response rates for ACR20/50/70, MDA, PASI75/90/100, sIGA, enthesitis resolution, and dactylitis resolution in patients treated with RINVOQ 15 mg were maintained through Week 56.

*Radiographic Response*

In SELECT-PsA 1, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Total Sharp Score (mTSS) and its components, the erosion score and the joint space narrowing score, at Week 24.

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Week 24 (Table 11). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0.5) was higher with RINVOQ 15 mg compared to placebo at Week 24.

**Table 11: Radiographic Changes in SELECT-PsA 1**

| Treatment Group | PBO | UPA 15 mg | ADA 40 mg |
|---|---|---|---|
| **Modified Total Sharp Score, mean change from baseline** | | | |
| Week 24 | 0.25 | -0.04[c] | 0.01 |
| Week 56[a] | 0.44 | -0.05[d] | -0.06 |
| **Erosion Score, mean change from baseline** | | | |
| Week 24 | 0.12 | -0.03[d] | 0.01 |
| Week 56[a] | 0.30 | -0.03[d] | -0.05 |
| **Joint Space Narrowing Score, mean change from baseline** | | | |
| Week 24 | 0.10 | -0.00[d] | -0.02 |

| | | | |
|---|---|---|---|
| Week 56[a] | 0.14 | -0.03[d] | -0.03 |
| **Proportion of patients with no radiographic progression[b]** | | | |
| Week 24 | 92 | 96[d] | 95 |
| Week 56[a] | 89 | 97[d] | 94 |

Abbreviations: ADA = adalimumab; PBO = placebo; UPA= upadacitinib

[a] All placebo data at week 56 derived using linear extrapolation

[b] No progression defined as mTSS change ≤0.5

[c] p≤0.001 upadacitinib vs placebo comparison

[d] Upadacitinib vs placebo comparisons were not controlled for multiplicity.

*Physical Function Response and Health-Related Outcomes*

In both studies, patients treated with RINVOQ 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by HAQ-DI at Week 12 (Table 10), which was maintained through Week 56.

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

Health-related quality of life was assessed by SF-36. In both studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared to placebo at Week 12. Greater improvement was also observed compared to adalimumab. Greater improvement was observed in the Mental Component Summary score and all 8 domains of SF-36 (Physical Functioning, Bodily Pain, Vitality, Social Functioning, Role Physical, General Health, Role Emotional, and Mental Health) compared to placebo. Improvements from baseline were maintained through Week 56 in both studies.

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

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

Among patients with psoriatic spondylitis, in both studies patients treated with RINVOQ 15 mg showed improvements from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

and Ankylosing Spondylitis Disease Activity Scores (ASDAS) compared to placebo at Week 24. Improvements from baseline were maintained through Week 56 in both studies.

*Ankylosing Spondylitis*

The efficacy and safety of RINVOQ 15 mg once daily were assessed in a randomized, double-blind, multicenter, placebo-controlled study in patients 18 years of age or older with active ankylosing spondylitis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and Patient's Assessment of Total Back Pain score ≥4 (Table 12). The study included an open-label extension for up to 2 years after a double-blind, placebo-controlled 14-week period.

**Table 12: Clinical Trial Summary**

| **Study Name** | **Population (n)** | **Treatment Arms** | **Key Outcome Measures** |
|---|---|---|---|
| SELECT-AXIS 1 | NSAID-IR[a,b] bDMARD-naïve (187) | • Upadacitinib 15 mg<br>• Placebo | Primary Endpoint:<br>• ASAS40 at Week 14 |
| | | | Key Secondary Endpoints at Week 14:<br>• ASAS Partial Remission<br>• BASDAI 50<br>• ASDAS-CRP<br>• BASFI<br>• SPARCC MRI score (spine)<br>• ASQoL<br>• BASMI<br>• MASES<br>• WPAI<br>• ASAS HI |

Abbreviations: ASAS40 = Assessment of SpondyloArthritis international Society ≥40% improvement; ASAS HI = ASAS Health Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; ASQoL = AS Quality of Life Questionnaire; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitits Metrology Index; bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; NSAID = Nonsteroidal

Anti-inflammatory Drug; SPARCC MRI = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging; WPAI = Work Productivity and Activity Impairment

[a] Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindications for NSAIDs.

[b] At baseline, approximately 16% of the patients were on a concomitant csDMARD.

*Clinical Response*

In SELECT-AXIS 1, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 13, Figure 2). Greater responses were seen as early as Week 2 for ASAS40.

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

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

**Figure 2: Percent of Patients Achieving ASAS40**

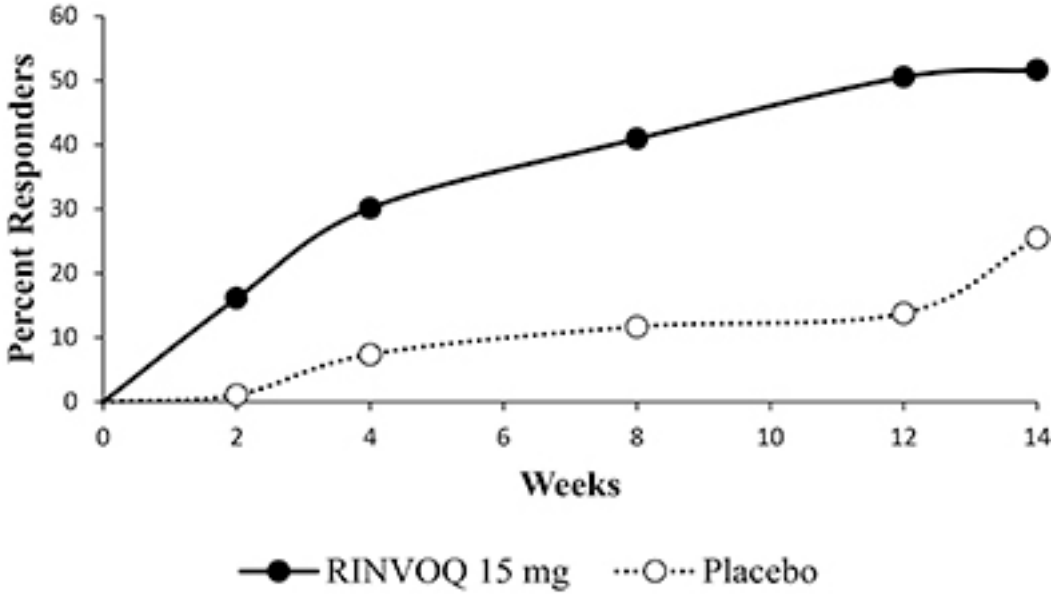



**Table 13: Clinical Response in SELECT-AXIS 1**

| Treatment Group | **PBO** | **UPA 15 mg** |
|---|---|---|
| N | 94 | 93 |
| **ASAS40 (% of patients)** | | |

| | | |
|---|---|---|
| Week 14 | 25.5 | 51.6[a] |
| **ASAS20 (% of patients)** | | |
| Week 14 | 40.4 | 64.5[c] |
| **ASAS Partial Remission (% of patients)** | | |
| Week 14 | 1.1 | 19.4[a] |
| **BASDAI 50 (% of patients)** | | |
| Week 14 | 23.4 | 45.2[b] |
| **Change from baseline in ASDAS-CRP** | | |
| Week 14 | -0.54 | -1.45[a] |

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

[a] p≤0.001 upadacitinib vs placebo comparison

[b] p≤0.01 upadacitinib vs placebo comparison

[c] Upadacitinib vs placebo comparisons were not controlled for multiplicity.

[d] post-hoc analysis

For binary endpoints, Week 14 results are based on non-responder imputation analysis. For continuous endpoints, Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measure analysis.

Response rates for ASAS40, ASAS20, ASAS partial remission, BASDAI 50, ASDAS Inactive Disease, ASDAS Low Disease Activity, and change from baseline in ASDAS-CRP in patients treated with RINVOQ 15 mg were maintained through Week 64.

Improvements were observed in pre-defined key secondary endpoints of BASMI, MASES, ASQoL, ASAS HI, and WPAI compared to placebo, but these were not statistically significant in the multiplicity adjusted analyses.

*Physical Function and Health-Related Outcomes*

Significant improvement in physical function as assessed by change in BASFI score from baseline at Week 14 was observed in patients treated with RINVOQ 15 mg (-2.29) compared to placebo (-1.30). This improvement was maintained through Week 64.

Patients treated with RINVOQ 15 mg showed greater improvement in back pain as assessed by the Total Back Pain component of ASAS response compared to placebo at Week 14.
Improvement was demonstrated for nocturnal back pain compared to placebo at Week 14 and was observed as early as Week 2. Improvements were also observed in peripheral pain and swelling (assessed by BASDAI question 3 on overall pain in joints other than in the neck, back, or hips) compared to placebo at Week 14. Pain improvements were maintained through Week 64.

*Objective Measure of Inflammation*
Signs of inflammation were assessed by MRI and expressed as change from baseline in the SPARCC score for spine. At Week 14, significant improvement of inflammatory signs in the spine was observed in patients treated with RINVOQ 15 mg compared to placebo.

*Atopic Dermatitis*

The efficacy and safety of RINVOQ 15 mg and 30 mg once daily was assessed in three Phase 3 randomized, double-blind, multicenter studies (MEASURE UP 1, MEASURE UP 2 and AD UP) in a total of 2584 patients (12 years of age and older) (Table 14). RINVOQ was evaluated in 344 adolescent and 2240 adult patients with moderate to severe atopic dermatitis (AD) not adequately controlled by topical medication(s). At baseline, patients had to have all the following: an Investigator's Global Assessment (vIGA-AD) score ≥3 in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 (composite score assessing extent and severity of erythema, edema/papulation, scratches and lichenification across 4 different body sites), a minimum body surface area (BSA) involvement of ≥10%, and weekly average Worst Pruritus Numerical Rating Scale (NRS) ≥4.
In all three studies, patients received RINVOQ once daily doses of 15 mg, 30 mg or matching placebo for 16 weeks. In the AD UP study, patients also received concomitant topical corticosteroids (TCS). Following completion of the double-blinded period, patients originally randomized to RINVOQ were to continue receiving the same dose until week 136. Patients in the placebo group were re-randomized in a 1:1 ratio to receive RINVOQ 15 mg or 30 mg until week 136.

**Table 14. Clinical Trial Summary**

| **Study Name** | **Treatment Arms** | **Key Outcome Measures** |
|---|---|---|
| MEASURE UP 1 and | • Upadacitinib 15 mg | Co-Primary Endpoints at Week 16:<br>• EASI 75<br>• vIGA-AD 0/1 |

| | | |
|---|---|---|
| MEASURE UP 2 | • Upadacitinib 30 mg<br>• Placebo | Key Secondary Endpoints (at Week 16 except where noted)<br>• EASI 90/100<br>• EASI 75 at Week 2<br>• % change in EASI<br>• % change in SCORAD<br>• Worst Pruritus NRS improvement ≥ 4 at Week 1 and 16<br>• Worst Pruritus NRS improvement ≥ 4 at Day 2 (30 mg), Day 3 (15 mg)<br>• % change in Worst Pruritus NRS<br>• EASI increase ≥ 6.6 points (flare) during double-blind period<br>• ADerm-SS TSS-7 improvement ≥ 28<br>• ADerm-SS Skin Pain improvement ≥ 4<br>• ADerm-IS Sleep improvement ≥ 12<br>• ADerm-IS Emotional State improvement ≥ 11<br>• ADerm-IS Daily Activities improvement ≥ 14<br>• POEM improvement ≥ 4<br>• HADS-A < 8 and HADS-D < 8<br>• DLQI 0/1<br>• DLQI improvement ≥ 4 |
| AD UP | • Upadacitinib 15 mg + TCS<br>• Upadacitinib 30 mg + TCS<br>• Placebo + TCS | Co-Primary Endpoints at Week 16:<br>• EASI 75<br>• vIGA-AD 0/1<br>Key Secondary Endpoints (at Week 16 except where noted)<br>• EASI 75 at Week 2 and 4<br>• EASI 90 at Week 4 and 16<br>• EASI 100 (30 mg)<br>• % change in EASI<br>• Worst Pruritus NRS improvement ≥ 4 at Week 1, 4 and 16<br>• % change in Worst Pruritus NRS |
| Abbreviations: SCORAD = SCORing Atopic Dermatitis, POEM: Patient Oriented Eczema Measure, DLQI: Dermatology Life Quality Index, HADS: Hospital Anxiety and Depression Scale, ADerm-SS = Atopic Dermatitis Symptom Scale, ADerm-IS: Atopic Dermatitis Impact Scale | | |

*Baseline characteristics*

In the monotherapy studies (MEASURE UP 1 and 2), 50.0% of patients had a baseline a vIGA-AD score of 3 (moderate) and 50.0% of patients had a 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 monotherapy studies, across all treatment groups, the mean age was 33.8, the mean weight was 74.8 kg, 44.9% were female, 67.3% were white, 22.9% were Asian, and 6.3% were black.

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 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%. In the AD UP study, across all treatment groups, the mean age was 34.1, the mean weight was 75.5 kg, 39.3% were female, 71.8% were white, 20.5% were Asian, and 5.5% were black.

*Clinical Response*

*Monotherapy Studies (MEASURE UP 1 AND MEASURE UP 2)*

In the MEASURE UP studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved vIGA-AD 0 or 1 response and achieved EASI 75 compared to placebo at week 16 (Table 15). A rapid improvement in skin clearance (defined as EASI 75 by week 2) was achieved for RINVOQ 15 mg compared to placebo ($p < 0.001$).

A significantly greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful improvement in itch (defined as a ≥ 4-point reduction in the Worst Pruritus NRS) compared to placebo at week 16. Rapid improvement in itch (defined as a ≥ 4-point reduction in Worst Pruritus NRS by week 1) was achieved for RINVOQ 15 mg compared to placebo ($p < 0.001$), with differences observed as early as 2 days after initiating RINVOQ 15 mg (Day 3, $p < 0.001$).

A significantly smaller proportion of patients treated with RINVOQ 15 mg had a disease flare, defined as a clinically meaningful worsening of disease (increase in EASI by ≥ 6.6), during the initial 16 weeks of treatment compared to placebo ($p < 0.001$).

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

**Table 15: Efficacy results of RINVOQ monotherapy studies at week 16**

| **Study** | **MEASURE UP 1** | | **MEASURE UP 2** | |
|---|---|---|---|---|
| Treatment Group | PBO | UPA 15 mg | PBO | UPA 15 mg |
| Number of subjects randomized | 281 | 281 | 278 | 276 |
| **% responders** | | | | |
| vIGA-AD 0/1[a,b] | 8.4 | 48.1[f] | 4.7% | 38.8[f] |
| EASI 75[a] | 16.3 | 69.6[f] | 13.3% | 60.1[f] |

| | | | | |
|---|---|---|---|---|
| EASI 90[a] | 8.1 | 53.1[f] | 5.4 | 42.4[f] |
| EASI 100[a] | 1.8 | 16.7[f] | 0.7 | 14.1[f] |
| Worst Pruritus NRS[c] *(≥ 4-point improvement)* | 11.8 N=272 | 52.2[f] N=274 | 9.1 N=274 | 41.9[f] N=270 |
| Worst Pruritus NRS 0 or 1[d] | 5.5 N=275 | 36.6[g] N=279 | 4.3 N=277 | 26.9[g] N=275 |
| **Mean percent change (SE)[e]** | | | | |
| EASI | -40.7 (2.28) | -80.2[f] (1.91) | -34.5 (2.59) | -74.1[f] (2.20) |
| SCORAD | -32.7 (2.33) | -65.7[f] (1.78) | -28.4 (2.50) | -57.9[f] (2.01) |
| Worst Pruritus NRS | -26.1 (5.41) | -62.8[f] (4.49) | -17.0 (2.73) | -51.2[f] (2.34) |

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

[a] Based on number of subjects randomized

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

[c] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4

[d] N = number of patients whose baseline Worst Pruritus NRS is > 1

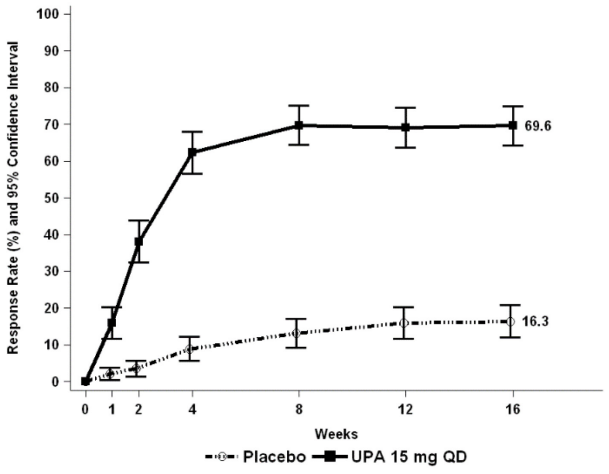
[e] % change = least squares mean percent change relative to baseline

[f] multiplicity-controlled p < 0.001 upadacitinib vs placebo comparison

[g] nominal p<0.001 upadacitinib vs placebo comparison

**Figure 5: Proportion of patients achieving an EASI 75 response in monotherapy studies**

**MEASURE UP 1**




**MEASURE UP 2**

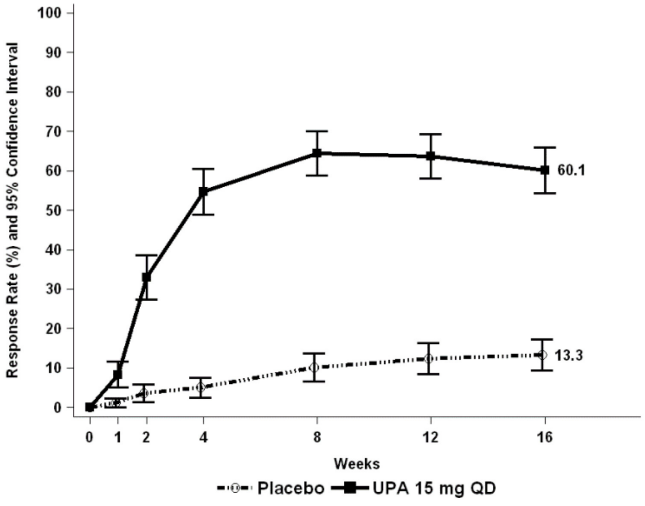
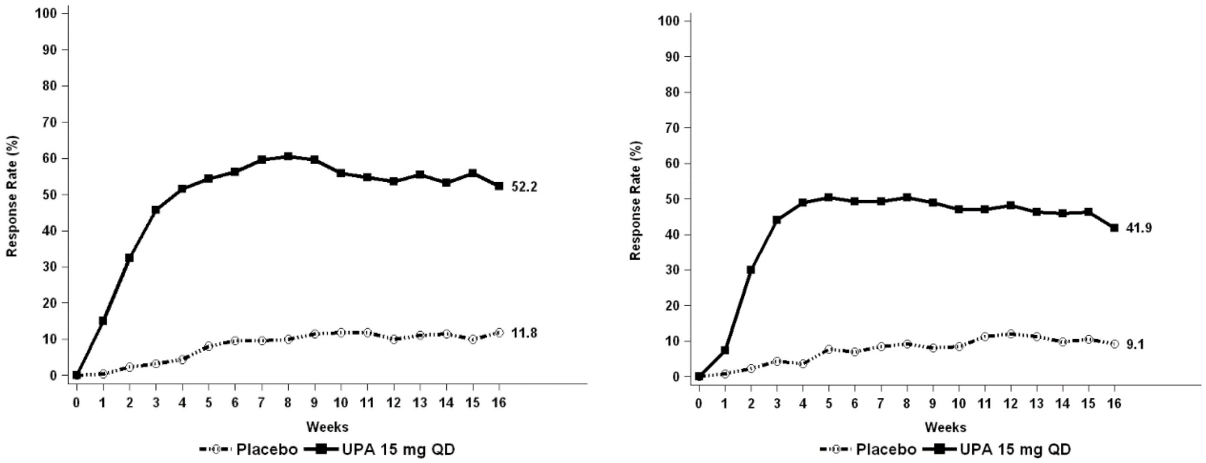


**Figure 6: Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in monotherapy studies**

**MEASURE UP 1** **MEASURE UP 2**




Treatment effects in subgroups (weight, age, gender, race, and prior systemic treatment with immunosuppressants) in both studies were consistent with the results in the overall study population. In both studies, results at week 16 continued to be observed through week 52 in patients treated with RINVOQ 15 mg.

*Concomitant TCS Study (AD UP)*

In AD UP, a significantly greater proportion of patients treated with RINVOQ 15 mg + TCS achieved vIGA-AD 0 or 1 response and achieved EASI 75 compared to placebo + TCS at week 16 (Table 16). A rapid improvement in skin clearance (defined as EASI 75 by week 2) was achieved compared to placebo + TCS ($p < 0.001$). In addition, a higher EASI 90 response rate was achieved at week 4 compared to placebo + TCS ($p < 0.001$).

A significantly greater proportion of patients treated with RINVOQ 15 mg + TCS achieved a clinically meaningful improvement in itch (defined as a ≥ 4-point reduction in the Worst Pruritus NRS) compared to placebo + TCS at week 16. A rapid improvement in itch (defined as a ≥ 4-point reduction in Worst Pruritus NRS by week 1) was achieved compared to placebo + TCS ($p < 0.001$).

Figure 7 and Figure 8 show proportion of patients achieving an EASI 75 response and the proportion of patients with ≥4-point improvement in the Worst Pruritus NRS, respectively up to week 16.

**Table 16: Efficacy results of RINVOQ + concomitant TCS at week 16**

| **Treatment Group** | **Placebo + TCS** | **UPA 15 mg + TCS** |
|---|---|---|
| Number of subjects randomized | 304 | 300 |

| **% responders** | | |
|---|---|---|
| vIGA-AD 0/1[a,b] | 10.9 | 39.6[f] |
| EASI 75[a] | 26.4 | 64.6[f] |
| EASI 90[a] | 13.2 | 42.8[f] |
| EASI 100[a] | 1.3 | 12.0 [g] |
| Worst Pruritus NRS[c]<br>*(≥ 4-point improvement)* | 15.0<br>N=294 | 51.7[f]<br>N=288 |
| Worst Pruritus NRS 0 or 1[d] | 7.3<br>N=300 | 33.1[g]<br>N=296 |
| **Mean percent change (SE)[e]** | | |
| EASI | -45.9 (2.16) | -78.0[f] (1.98) |
| SCORAD | -33.6 (1.90) | -61.2[g] (1.70) |
| Worst Pruritus NRS | -25.1 (3.35) | -58.1[f] (3.11) |

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

[a] Based on number of subjects randomized

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

[c] N = number of patients whose baseline Worst Pruritus NRS is ≥ 4

[d] N = number of patients whose baseline Worst Pruritus NRS is > 1

[e] % change = least squares mean percent change relative to baseline

[f] multiplicity-controlled p < 0.001 upadacitinib + TCS vs placebo + TCS comparison

[g] nominal p <0.001 upadacitinib + TCS vs placebo + TCS comparison

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

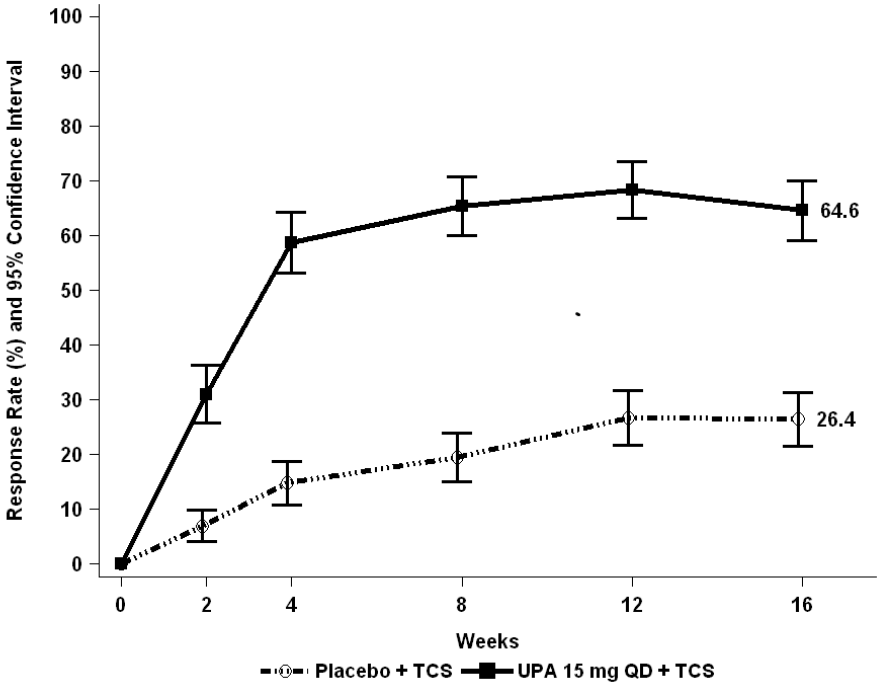
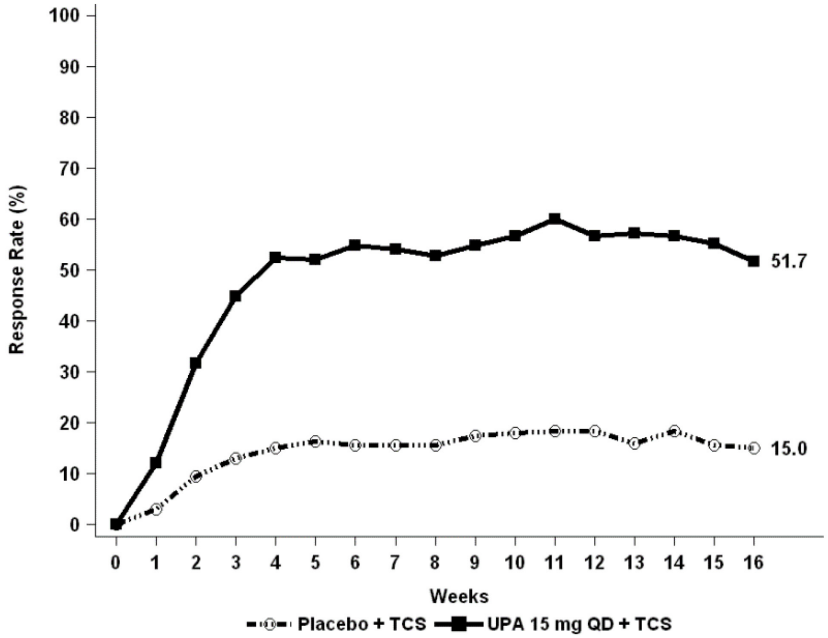



**Figure 8: Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in AD UP Study**




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

Subjects treated with RINVOQ 15 mg had significantly more days free of TCS use with a concurrent EASI 75 response (mean: 33.5) over the 16-week period, compared to placebo group (mean: 7.9 days).

Results at week 16 continued to be observed through week 52 in patients treated with RINVOQ 15 mg.

*Quality of Life/Patient reported outcomes*

In the MEASURE UP studies, a significantly greater proportion of patients treated with RINVOQ 15 mg reported clinically meaningful reductions in the symptoms of AD and the impact of AD on health-related quality of life compared to placebo at week 16 (Table 17). A significantly greater proportion of patients treated with RINVOQ achieved clinically meaningful reductions in AD symptom severity as measured by ADerm-SS TSS-7 and ADerm-SS Skin Pain compared to placebo at week 16. A greater proportion of patients treated with RINVOQ achieved clinically meaningful reductions in the patient-reported effects of AD on sleep, daily activities and emotional state as measured by the ADerm-IS domain scores compared to placebo at week 16. Similarly, compared to placebo at week 16, a greater proportion of patients treated with RINVOQ achieved clinically meaningful improvements in AD symptom frequency and health-related quality of life as measured by the POEM and DLQI. Anxiety and depression symptoms as measured by the HADS score were significantly reduced; in patients with baseline HADS-anxiety or HADS-depression subscale scores ≥ 8 (the cut-off value for anxiety or depression), a greater proportion of patients in the RINVOQ 15 mg group achieved HADS-anxiety and HADS-depression scores < 8 at week 16 compared to placebo (Table 17).

**Table 17: Patient-reported outcomes results of RINVOQ monotherapy studies at week 16**

| **Study** | **MEASURE UP 1** | | **MEASURE UP 2** | |
|---|---|---|---|---|
| Treatment group | PBO | UPA 15 mg | PBO | UPA 15 mg |
| Number of subjects randomized | 281 | 281 | 278 | 276 |
| **% responders** | | | | |
| ADerm-SS TSS-7 *(≥ 28-point improvement)* [a,b] | 15.0 N=226 | 53.6[h] N=233 | 12.7% N=244 | 53.0[h] N=230 |
| ADerm-SS Skin Pain *(≥ 4-point improvement)*[a] | 15.0 N=233 | 53.6 [h] N=237 | 13.4% N=247 | 49.4[h] N=237 |
| ADerm-IS Sleep *(≥ 12-point improvement)* [a,c] | 13.2 N=220 | 55.0[h] N=218 | 12.4% N=233 | 50.2[h] N=219 |
| ADerm-IS Daily Activities | 20.3 | 65.0[h] | 18.9% | 57.0[h] |

| | | | | |
|---|---|---|---|---|
| *(≥ 14-point improvement)*[a,d] | N=197 | N=203 | N=227 | N=207 |
| ADerm-IS Emotional State<br>*(≥ 11-point improvement)* [a,e] | 19.8<br>N=212 | 62.6[h]<br>N=227 | 16.7%<br>N=234 | 57.0[h]<br>N=228 |
| DLQI<br>*(DLQI 0/1)*[f] | 4.4<br>N=252 | 30.3[h]<br>N=258 | 4.7%<br>N=257 | 23.8[h]<br>N=252 |
| DLQI<br>*(≥ 4-point improvement)* [a] | 29.0<br>N=250 | 75.4[h]<br>N=254 | 28.4%<br>N=250 | 71.7[h]<br>N=251 |
| POEM<br>*(≥ 4-point improvement)* [a] | 22.8%<br>N=276 | 75.0[h]<br>N=278 | 28.7%<br>N=268 | 70.9[h]<br>N=268 |
| HADS<br>*(HADS-A < 8 and HADS-D < 8)* [g] | 14.3<br>N=126 | 45.5[h]<br>N=145 | 11.4%<br>N=140 | 46.0[h]<br>N=137 |

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

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

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

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

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

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

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

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

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

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

**Pharmacokinetics**

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

*Absorption*

Following oral administration of upadacitinib extended-release formulation, upadacitinib is absorbed with a median $T_{max}$ of 2 to 4 hours.
Coadministration of upadacitinib with a high-fat meal had no clinically relevant effect on upadacitinib exposures (increased $AUC_{inf}$ 29% and $C_{max}$ 39%). In clinical trials, RINVOQ was administered without regard to meals (see «Dosage and Administration»).

*Distribution*

Upadacitinib is 52% bound to plasma proteins. Upadacitinib has a blood to plasma ratio of 1.0 indicating that it partitions similarly between plasma and blood cellular components.

*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, upadacitinib accounted for 79% of the total radioactivity in plasma while the two main metabolites detected (products of monooxidation followed by glucuronidation or monooxidation followed by ring opening) accounted for 13% and 7.1% of the total plasma radioactivity, respectively. 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 feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours.

*Kinetics in specific patient groups*

*Hepatic impairment*

Upadacitinib AUC was 28% and 24% higher in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib $C_{max}$ was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C).

*Renal impairment*

Mild, moderate or severe renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild (estimated glomerular filtration rate 60 to 89 mL/min/1.73 $m^2$), moderate (estimated glomerular filtration rate 30 to 59 mL/min/1.73 $m^2$), and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 $m^2$) renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib $C_{max}$ was similar in subjects with normal and impaired renal function. Upadacitinib was not studied in subjects with end stage renal impairment (estimated glomerular filtration rate <15 ml/min/1.73 $m^2$) or in subjects undergoing renal dialysis.

*Other Intrinsic Factors*

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

**Preclinical data**

In nonclinical studies in animals, decreases in circulating lymphocytes and decreased cellularity of lymphoid tissues, as well as suppression of erythropoiesis, were observed in rats and dogs at clinically relevant doses. Secondary effects related to opportunistic infections, such as demodicosis (mange) in dogs, were observed at exposures approximately two times the expected exposures (AUC) at the clinical dose of 15 mg and at similar exposures to the expected exposure at the dose of 30 mg (not approved in Switzerland).

*Mutagenicity*

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

*Carcinogenicity*

Upadacitinib, at exposure levels approximately 4 and 10 times the clinical dose of 15 mg (on an AUC basis at oral doses in male and female rats at 15 and 20 mg/kg/day, respectively) and 2 and 5 times the dose of 30 mg (not approved in Switzerland), was not carcinogenic based on 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.

*Reproductive toxicity*

Upadacitinib is teratogenic in both rats and rabbits when given at exposures of 1.6 or 15 times the clinical dose of 15 mg and 0.8 and 7.6 times the dose of 30 mg (not approved in Switzerland) for rats and rabbits, respectively (on an AUC basis at maternal oral doses of 4 mg/kg/day or 25 mg/kg/day, respectively). Effects in rats included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and an increase in bent bones of the fore- and hind-limbs. Developmental effects in rabbits included an increase in post-implantation losses, increase in total and early resorptions, lower fetal body weights, and increased incidence of cardiac malformations. In a pre-/postnatal development study in rats, there were no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on their offspring.

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

**Other information**

*Shelf life*

The drug product can be used only up to the expiry date identified by «EXP».

*Special precautions for storage*

Do not store above 25 °C.
Store in the original blister to protect from moisture.
Keep out of reach of children.

**Authorisation number**

67257 (Swissmedic)

**Packs**

RINVOQ 15 mg: blister with 28 prolonged-release tablets (B)

**Marketing authorisation holder**

AbbVie AG, 6330 Cham

**Date of revision of the text**

October 2021