

Date: 31 May 2021

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Rinvoq

International non-proprietary name: upadacitinib, 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: approved on 23 March 2021

Note:

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

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

ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying anti-rheumatic drug
cDMARD	conventional disease-modifying anti-rheumatic drug
C _{max}	Maximum observed plasma/serum concentration of drug
CPK	Creatine phosphokinase
CYP	Cytochrome P450
DMARD	Disease-modifying anti-rheumatic drug
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HAQ	Health Assessment Questionnaire
ICH	International Council for Harmonisation
IFN	Interferon
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MTX	Methotrexate
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PsA	Psoriatic arthritis
PSP	Pediatric Study Plan (US-FDA)
RA	Rheumatoid arthritis
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
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

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 used to treat adults with active psoriatic arthritis who have responded poorly to, or cannot tolerate, treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with non-biological DMARDs. RINVOQ inhibits the progression of structural damage and improves physical functions.

2.2.2 Approved Indication

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.

2.2.3 Requested Dosage

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

The recommended dose is 15 mg administered once daily, with or without food.

RINVOQ tablets should be swallowed whole and should not be crushed or chewed.

It is recommended not to use RINVOQ in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm³, an absolute neutrophil count (ANC) less than 1000 cells/mm³ or a haemoglobin level less than 8 g/L.

If a patient develops a serious infection, RINVOQ treatment should be interrupted until the infection is controlled.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	16 June 2020
Formal control completed	25 June 2020
List of Questions (LoQ)	29 September 2020
Answers to LoQ	25 November 2020
Predecision	2 February 2021
Answers to Predecision	18 February 2021
Final Decision	23 March 2021
Decision	approval

3 Medical Context

Psoriatic arthritis (PsA) belongs to the disease group of spondyloarthritides (SpA). It can manifest itself predominantly as a peripheral (as mono/oligoarthritis, or symmetrical polyarthritis) or axial condition (as spondylitis, sacroiliitis and/or arthritis affecting the shoulders or hips). PsA is diagnosed based on clinical findings, including current, or a history of, skin/nail lesions.

Treatment aims at improving the symptoms/findings of the arthritis (peripheral/axial), improving function, preventing structural damage, and preventing disability.

Initial treatment options are non-steroidal anti-inflammatory drugs (NSAID) and local corticosteroid injections, followed by cDMARDs (primarily methotrexate, leflunomide, sulfasalazine or cyclosporine A) and, when the response is inadequate, by biologics (primarily tumour necrosis factor inhibitors).

Biologic agents authorised to date for psoriatic arthritis:

<i>Active substance</i>	<i>Active substance class</i>
Infliximab	Anti-TNF α
Ustekinumab	Anti-IL-12/23
Certolizumab pegol	Anti-TNF α
Etanercept	Anti-TNF α
Secukinumab	Anti-IL-17A
Adalimumab	Anti-TNF α
Golimumab	Anti-TNF α
Ixekizumab	Anti-IL-17A

Janus kinase inhibitors

Janus kinases (JAKs) play an important role in the intracellular signal transduction of cytokine receptors (particularly IFN) and growth factors. The JAK family comprises JAK 1, 2 and 3 and tyrosine kinase 2. JAK1 is relevant mainly to inflammatory cytokines, JAK2 to erythropoiesis, myelopoiesis and thrombopoiesis, and JAK3 to lymphocyte function, in particular NK cells.

To date, the following risks have been identified:

- Infections
- Malignancies (particularly including EBV-associated lymphoproliferative disorders during combined administration with calcineurin antagonists),
- Major adverse cardiovascular events
- Venous thromboembolic events
- Gastrointestinal perforations
- Decreased lymphocytes, neutrophils and haemoglobin
- Hyperlipidaemia
- Elevated CPK
- Hepatic/renal impairment

4 Nonclinical Aspects

Additional nonclinical studies were not conducted to support the new indication of psoriatic arthritis for Rinvoq (active pharmaceutical ingredient: upadacitinib). This is acceptable since the extended indication is based on clinical data and there are no changes to the already approved treatment scheme or dose. The updated ERA does not indicate an environmental risk. From the preclinical standpoint, there are no objections to the approval of the requested new indication.

5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology, Dose Finding and Dose Recommendation

For the PK analysis in PsA patients, upadacitinib levels were measured during the pivotal studies at different times after the start of treatment. The results were similar to those reported for RA patients. Therefore, the PK information and conclusions relating to special patient populations and interactions on upadacitinib in the treatment of RA also apply to its use in the treatment of PsA.

The exposure response analysis shows that a 7-8% higher ACR 50/70 response would be achieved with the higher dose. However, regarding the other endpoints, it is expected that the plateau of full efficacy is reached with the 15 mg dose. In view of the increased side effects observed with the higher 30 mg dose, the lower 15 mg dose, which is already authorised for RA, was selected.

5.2 Efficacy

Two pivotal studies, of which the design was agreed with the EMA, were submitted. Both studies recruited patients aged 18 years and over with moderate to severe PsA. In both studies, prior treatment with non-biologic DMARDs could be continued unchanged, and both included two phases.

First phase:

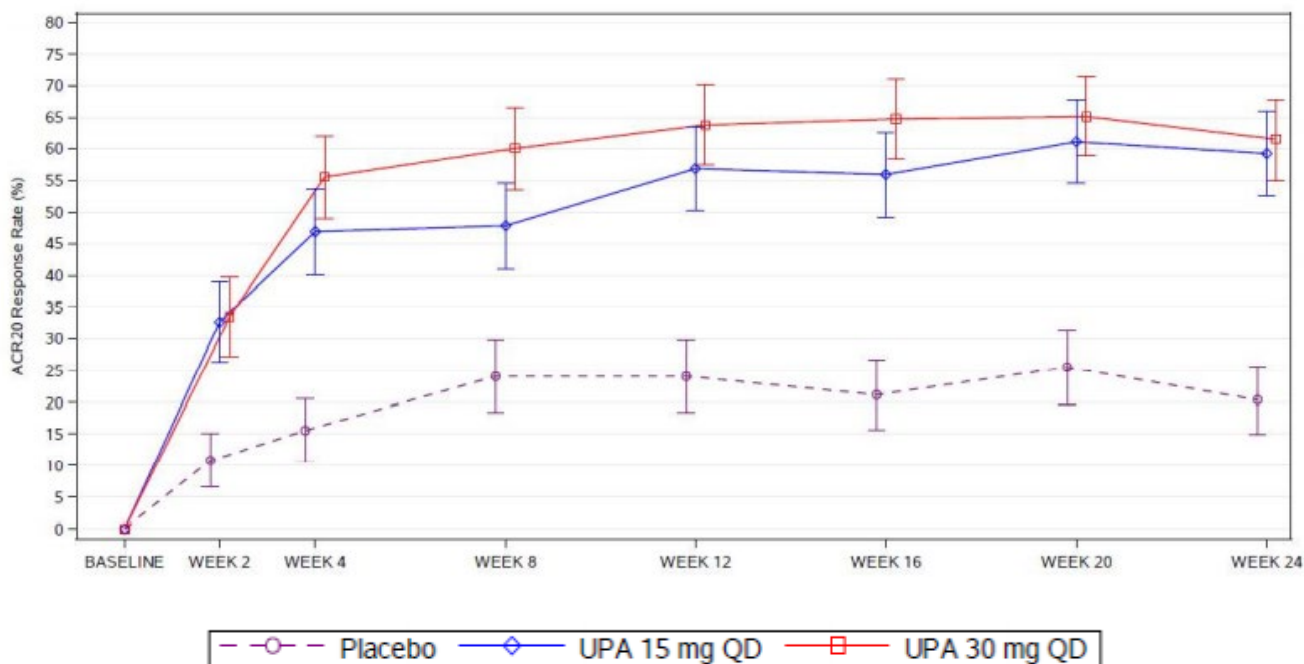
Both studies lasted 24 weeks and included a randomized, double-blind, placebo-controlled, parallel-group comparison – in one of the studies with an additional active comparison.

Study	Pretreatment	Concomitant treatment	Comparison	Radiolog. endpoints
M15-554	bDMARD non-responders: 46.6% adalimumab 41.7% etanercept	optionally cDMARD: 48.8% with cDMARD 39.3% with MTX	– UPA 15 mg (N=211) – UPA 30 mg (N=219) – Placebo (N=212)	no
M15-572	c-DMARD non-responders: 91.7% MTX	optionally cDMARD 82.3% with cDMARD 69.0% with MTX	– UPA 15 mg (N=430) – UPA 30 mg (N=423) – Adalimumab* (N=429) – Placebo (N=423) * as authorised for PsA	yes

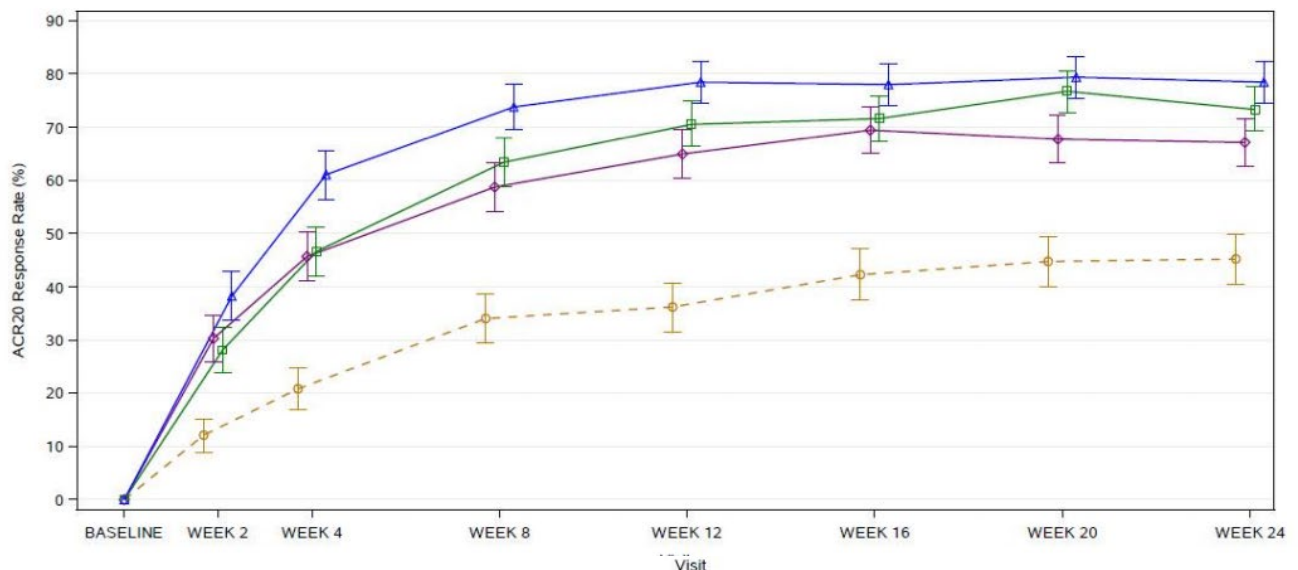
Endpoints: The primary endpoint in both studies was the ACR 20 response rate in week 12. Secondary endpoints controlled for multiple testing included the HAQ, recommended by the current EMA Guideline to capture functional improvement. In addition, in study M15-572, the Sharp score, recommended to measure structural improvement, in week 24 was included as secondary endpoint.

Results: In both studies, a statistically significant benefit over placebo was described for both upadacitinib doses in the respective overall population for both the primary endpoint and the secondary endpoints of inhibiting progression of structural degradation and improvement of physical functioning. In these respects, also non-inferiority, but not superiority, of upadacitinib versus adalimumab could be shown.

ACR 20 response rate after 12 weeks in study M15-554:



ACR 20 response rate after 12 weeks in study M15-572:



Number of Subjects at Each Visit	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo	423	423	423	423	423	423	423	423
ADA 40 mg EOW	429	429	429	429	429	429	429	429
UPA 15 mg QD	429	429	429	429	429	429	429	429
UPA 30 mg QD	423	423	423	423	423	423	423	423

Positive results regarding the primary endpoint were also shown in all investigated subgroups and particularly also for patients without concomitant non-biologic DMARDs; analyses relating to structural improvement were not available for this subgroup (in fact, conclusive results would hardly be expected here in view of the small number of patients investigated).

As regards psoriatic spondylitis and skin activity, an improvement versus placebo was described (e.g. BASDAI and PASI responses, however, this was not controlled for multiple testing).

Second phase:

The second phase is an ongoing open-label, long-term extension study lasting up to 3 years, during which the patients treated with placebo in the first phase could switch to upadacitinib 15 mg or upadacitinib 30 mg according to an initial randomisation. For this phase, safety data, but not yet efficacy data, have been submitted.

5.3 Safety

Including the open-label, long-term extension phases of the studies, a total of 1827 PsA patients were exposed to upadacitinib 15 mg or 30 mg, corresponding to 1639 patient-years. The development programme permitted controlled comparisons of upadacitinib 15 mg and upadacitinib 30 mg with placebo (in each case at least 600 patients and 250 patient-years) and with adalimumab (at least 400 patients with just under 190 patient-years).

In total, 2 deaths were recorded for upadacitinib 30 mg and 1 death in each case for upadacitinib 15 mg and placebo. Apart from a pancytopenia for upadacitinib 30 mg, the cases are not suggestive of a causal relationship with the study medication.

AEs of all severities were slightly more frequent, in a dose-dependent way, for upadacitinib than for placebo (upadacitinib 30 mg \geq upadacitinib 15 mg \geq adalimumab \geq placebo). The type of AEs resembled the pattern observed previously in the RA authorisation studies, with infections, gastrointestinal and thromboembolic complications and laboratory changes (CPK increases, elevated transaminase levels, mild anaemia/neutropenia, individual cases of lymphopenia, slight increase in creatinine and altered lipid levels).

5.4 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Both submitted pivotal studies described an advantage of upadacitinib over placebo in PsA in the investigated populations on standard efficacy endpoints. In a direct comparison, the effects described for upadacitinib in PsA were similar to those described for adalimumab, which has already been authorised for years for the treatment of PsA. Similar results for both active substances were also found in respect of safety and tolerability.

Based on the reviewed documentation, Swissmedic considers the benefit-risk balance of upadacitinib to be positive, when used as recommended for treating active psoriatic arthritis in the investigated population, i.e. adult patients who had responded inadequately to, or who were intolerant to, prior treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs).

5.5 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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.

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 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.

▼ 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).

Dosage/Administration

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

The recommended oral dose of RINVOQ is 15 mg once daily with or without food. RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed or chewed.

It is recommended that RINVOQ is not used in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm³, an absolute neutrophil count (ANC) less than 1000 cells/mm³ or who have hemoglobin levels less than 8 g/dL.

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 m²).

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

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»). 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 or inactivated 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. Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, depending on the situation this includes zoster/varicella vaccinations, in agreement with current immunization guidelines.

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 clinical features of a thromboembolic event occur, patients should be evaluated promptly, followed by appropriate treatment.

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/mm³). There was no clear association between low neutrophil counts and the occurrence of serious infections.

Lymphopenia - ALCs < 500 cells/mm³ 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 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

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (90% CI) ^a		Clinical Impact
				C _{max}	AUC	
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.

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (90% CI) ^a		Clinical Impact
				C _{max}	AUC	
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.

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 fetuses and in the heart in rabbit fetuses 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

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) occurring in $\geq 2\%$ 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 simplex and 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 tuberculosis 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 tuberculosis 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 VTE 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 VTE 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/mm³ 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/mm³. 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/mm³ 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.

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.

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)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Upadacitinib 30 mg • MTX <p>Monotherapy</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • ACR50 at Week 12 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Clinical Remission (DAS28-CRP <2.6) at Week 24 • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • Radiographic progression (ΔmTSS) at Week 24 • SF-36 PCS
SELECT-MONOTHERAPY	MTX-IR ^b (648)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Upadacitinib 30 mg • MTX <p>Monotherapy</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • ACR20 at Week 14 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Low Disease Activity (DAS28-CRP ≤3.2) at Week 14 • Clinical Remission (DAS 28-CRP <2.6) at Week 14 • Δ Physical Function (HAQ-DI) at Week 14 • SF-36 PCS • Morning stiffness
SELECT-NEXT	csDMARD-IR ^c		Primary Endpoint:

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	(661)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo <p>On background csDMARDs</p>	<ul style="list-style-type: none"> • ACR20 at Week 12 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Low Disease Activity (DAS28-CRP \leq3.2) at Week 12 • Clinical Remission (DAS28-CRP $<$2.6) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS • Morning stiffness • FACIT-F
SELECT-COMPARE	MTX-IR ^d (1629)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Placebo • Adalimumab 40 mg <p>On background MTX</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • ACR20 at Week 12 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Clinical Remission (DAS28-CRP $<$2.6) at Week 12 • Low Disease Activity (DAS28-CRP \leq3.2) at Week 12 • ACR50 vs adalimumab at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • Radiographic progression (ΔmTSS) at Week 26 • SF-36 PCS • Morning stiffness • FACIT-F
SELECT-BEYOND	bDMARD-IR ^e (499)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo <p>On background csDMARDs</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • ACR20 at Week 12 <p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> • Low Disease Activity (DAS28-CRP \leq3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS
<p>Abbreviations: ACR20 (or 50) = American College of Rheumatology \geq20% (or \geq50%) improvement, bDMARD = biologic disease-modifying anti-rheumatic drug; CR = Clinical Response, CRP = C-</p>			

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

^a Patients were naïve to MTX or received no more than 3 weekly MTX doses

^b Patients had inadequate response to MTX

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

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

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

Clinical Response

Remission and low disease activity

In 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

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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 ^l	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 ^l	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 ^l	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 ^l	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 ^l	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 ^l	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 ^l	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 ^l	15		
<p>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</p> <p>^a SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND</p> <p>^b SELECT-MONOTHERAPY</p> <p>^c SELECT-EARLY</p> <p>^d SELECT-COMPARE</p>											

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^e $p \leq 0.001$ upadacitinib vs placebo or MTX comparison
^f $p \leq 0.01$ upadacitinib vs placebo or MTX comparison
^g Upadacitinib vs placebo or MTX comparison (These comparisons are not controlled for multiplicity)
^h $p \leq 0.001$ upadacitinib 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,i}	-14	-8	-16 ^h
24 ^{d/} 26 ^e	-16	-19 ^h					-9	-18 ^{h,i}	-15		
Number of swollen joints (0-66)											
12 ^{b/} 14 ^c	-10	-12 ^h	-8	-11 ^h	-6	-9 ^h	-7	-11 ^{h,i}	-10	-6	-11 ^h
24 ^{d/} 26 ^e	-12	-14 ^h					-6	-12 ^{h,i}	-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,i}	-32		
Patient global assessment^f											
12 ^{b/} 14 ^c	-25	-35 ^h	-11	-23 ^h	-10	-30 ^h	-15	-30 ^{h,i}	-24	-10	-26 ^h
24 ^{d/} 26 ^e	-28	-39 ^h					-18	-36 ^{h,i}	-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

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24 ^{d/} 26 ^e	-0.6	-0.9 ^h					-0.3	-0.7 ^{h,i}	-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,i}	-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,i}	-9.2	-1.1	- 11.0 ^h
24 ^{d/} 26 ^e	-11.6	- 18.4 ^h					-1.5	-13.5 ^{h,i}	-10.3		
<p>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</p> <p>^a Data shown are mean</p> <p>^b SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND</p> <p>^c SELECT-MONOTHERAPY</p> <p>^d SELECT-EARLY</p> <p>^e SELECT-COMPARE</p> <p>^f Visual analog scale: 0 = best, 100 = worst</p> <p>^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.</p> <p>^h Upadacitinib vs placebo or MTX comparison (These comparisons are not controlled for multiplicity)</p> <p>ⁱ p≤0.001 upadacitinib vs placebo or MTX comparison</p> <p>^j p≤0.001 upadacitinib vs adalimumab comparison</p> <p>^k p≤0.01 upadacitinib vs adalimumab comparison</p> <p>^l Upadacitinib vs adalimumab comparison (These comparisons are not controlled for multiplicity)</p>											

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		
	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 $p \leq 0.001$ upadacitinib vs placebo or MTX comparison					
^f $p \leq 0.01$ upadacitinib vs placebo or MTX comparison					

⁹ 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

Product information for human medicinal products

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-PsA 1	Non-biologic DMARD-IR ^a (1705)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo • Adalimumab 40 mg 	Primary Endpoint: <ul style="list-style-type: none"> • ACR20 at Week 12
			Key Secondary Endpoints: <ul style="list-style-type: none"> • MDA at Week 24 • Resolution of enthesitis (LEI=0) and dactylitis (LDI=0) at Week 24 • PASI75 at Week 16 • sIGA at Week 16 • SAPS at Week 16 • Radiographic progression (ΔmTSS) at Week 24 • Δ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS at Week 12 • FACIT-F at Week 12 • ACR20, pain, and Δ Physical Function (HAQ-DI) vs adalimumab at Week 12
SELECT-PsA 2	bDMARD-IR ^b (642)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo 	Primary Endpoint: <ul style="list-style-type: none"> • ACR20 at Week 12
			Key Secondary Endpoints: <ul style="list-style-type: none"> • MDA at Week 24 • PASI75 at Week 16 • sIGA at Week 16 • SAPS at Week 16 • Δ Physical Function (HAQ-DI) at Week 12 • SF-36 PCS at Week 12 • FACIT-F at Week 12

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

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

^p 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

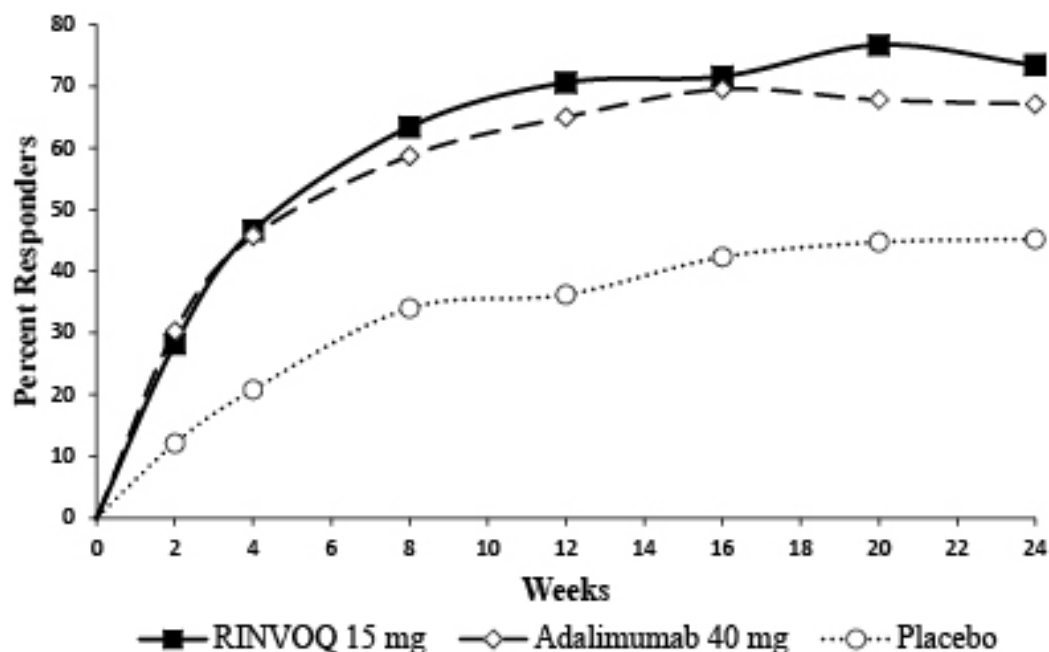


Table 9: Clinical response

Product information for human medicinal products

Study	SELECT-PsA 1 non-biologic DMARD-IR			SELECT-PsA 2 bDMARD-IR	
	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
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

Product information for human medicinal products

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
<p>Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology $\geq 20\%$ (or $\geq 50\%$ or $\geq 70\%$) improvement; ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; MDA = minimal disease activity; MTX = methotrexate; PASI75 (or 90 or 100) = $\geq 75\%$ (or $\geq 90\%$ or 100%) improvement in Psoriasis Area and Severity Index; PBO = placebo; sIGA = static Physician Global Assessment; UPA= upadacitinib</p> <p>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.</p> <p>^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)</p> <p>^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)</p> <p>^c In patients with $\geq 3\%$ BSA psoriasis at baseline (n=211, 214, and 211, respectively, for SELECT-PsA 1 and n=131 and 130, respectively, for SELECT-PsA 2)</p> <p>^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)</p> <p>^e $p \leq 0.001$ upadacitinib vs placebo comparison</p> <p>^f Upadacitinib vs placebo comparisons were not controlled for multiplicity.</p> <p>^g Upadacitinib vs adalimumab comparisons were not controlled for multiplicity.</p>					

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

Study	SELECT-PsA 1			SELECT-PsA 2	
	non-biologic DMARD-IR			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)					

Product information for human medicinal products

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
<p>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</p> <p>^a Numeric rating scale (NRS): 0 = best, 10 = worst</p> <p>^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.</p> <p>^c p≤0.001 upadacitinib vs placebo comparison</p> <p>^d Upadacitinib vs placebo comparisons were not controlled for multiplicity.</p> <p>^e Upadacitinib vs adalimumab comparisons were not controlled for multiplicity.</p>					

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 $p \leq 0.001$ 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

Product information for human medicinal products

SELECT- AXIS 1	NSAID-IR ^{a,b} bDMARD-naïve (187)	<ul style="list-style-type: none"> • Upadacitinib 15 mg • Placebo 	Primary Endpoint: <ul style="list-style-type: none"> • ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: <ul style="list-style-type: none"> • ASAS Partial Remission • BASDAI 50 • ASDAS-CRP • BASFI • SPARCC MRI score (spine) • ASQoL • BASMI • MASES • WPAI • ASAS HI
<p>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 Spondylitis 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</p> <p>^a Patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindications for NSAIDs.</p> <p>^b At baseline, approximately 16% of the patients were on a concomitant csDMARD.</p>			

Clinical Response

In SELECT-AXIS 1, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (Table 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

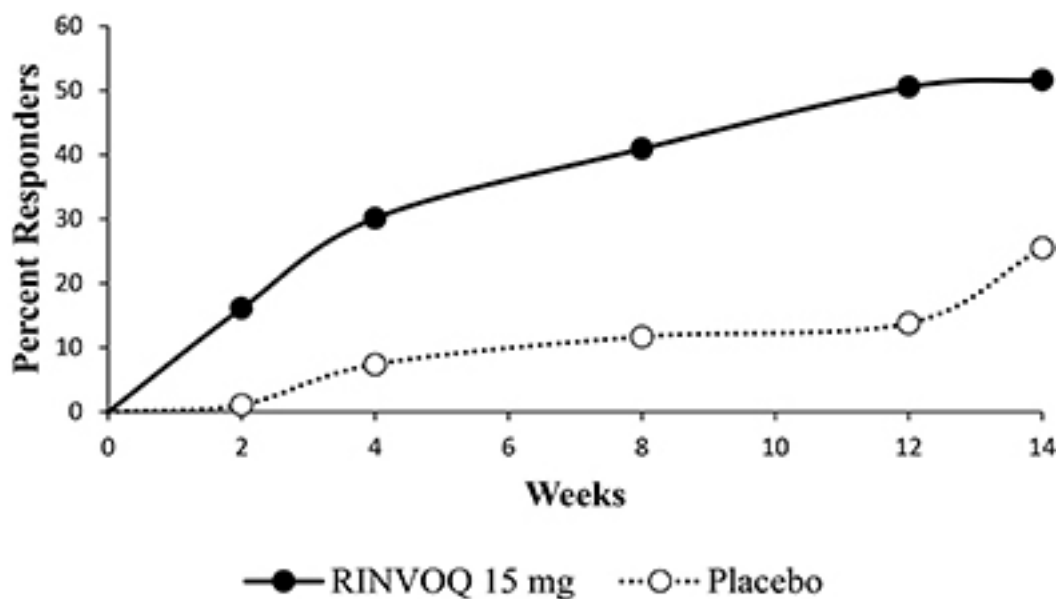


Table 13: Clinical Response in SELECT-AXIS 1

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 $\geq 20\%$ (or $\geq 40\%$) improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PBO = placebo; UPA= upadacitinib

^a $p \leq 0.001$ upadacitinib vs placebo comparison

^b $p \leq 0.01$ 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.

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

Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild (estimated glomerular filtration rate 60 to 89 mL/min/1.73 m²), moderate (estimated glomerular filtration rate 30 to 59 mL/min/1.73 m²), and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m²) 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 m²) 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, and ankylosing spondylitis 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.

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), 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 (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

March 2021