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.

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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

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	Axial Spondyloarthritis
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
cDMARD	Conventional disease-modifying anti-rheumatic drug
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CPK	Creatine phosphokinase
CYP	Cytochrome P450
DMARD	Disease-modifying antirheumatic drug
EBV	Epstein-Barr virus
ERA	Environmental Risk Assessment
FAS	Full analysis set
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
IFN	Interferon
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
nr-axSpA	Non-radiographic axial Spondyloarthritis
NO(A)EL	No Observed (Adverse) Effect Level
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RA	Rheumatoid arthritis
RMP	Risk Management Plan
SAE	Serious adverse event
SI	Sacroiliac
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SwissPAR	Swiss Public Assessment Report
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)

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TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UPA	Upadacitinib

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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 used for the treatment of adults with active ankylosing spondylitis who responded inadequately to conventional therapy.

2.2.2 Approved Indication

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

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 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 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	17 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

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3 Medical Context

Ankylosing spondylitis (AS; Bechterew's disease) belongs to the disease group of spondyloarthritides (SpA). AS is a chronic, inflammatory arthritis characterised by sacroiliitis, enthesitis and a pronounced tendency towards fusion of the sacroiliac joints and the spine. The exact cause of the disease is not known, but an autoimmune component is generally assumed to be present. 95% of the affected patients test positive for HLA-B27. The disease usually starts with pain in the sacroiliac joint, progresses gradually for years or decades, and can result in new bone formation and restricted movement. It can be accompanied by inflammatory bowel disease and recurrent episodes of iritis. It can take years before radiographic changes are detected. Radiographic classification criteria may therefore be suboptimal as they could potentially lead to the exclusion of patients in their early stages of the disease.

The aims of treatment are to alleviate the symptoms, preserve spinal flexibility, and reduce functional restrictions and complications of the disease. The key cornerstones of treatment are non-steroidal anti-inflammatory drugs (NSAIDs), exercise therapy and, since approximately 20 years, biologic agents such as tumour necrosis factor inhibitors. Biologic agents are used if the disease activity persists despite NSAID treatment. DMARDs (with the exception of sulfasalazine) and systemic corticosteroids, on the other hand, are of secondary importance.

Diagnosis: Nowadays, SpA is usually diagnosed based on the 'modified New York (mNY)' criteria, which require the presence of radiographic changes. Accordingly, axial SpA is subdivided into non-radiographic axial SpA (nr-axSpA) and classical AS (=radiographic axSpA). The term nr-axSpA refers to the group of patients without clearly visible structural lesions (to date) in the sacroiliac (SI) joints on a conventional radiograph.

Biologic agents used to date in spondyloarthritis:

In addition to five tumour necrosis factor inhibitors, two interleukin-17a-IgG1 antibodies have also been authorised for this indication.

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 for 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.

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4 Nonclinical Aspects

Additional nonclinical studies were not conducted to support the new indication of ankylosing spondylitis 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.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology, Dose Finding and Dose Recommendation

For the PK analysis in AS patients, upadacitinib levels were measured during the pivotal study 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 AS.
No AS-specific dose-finding studies were submitted. The selection of the same dose used for RA is justified by the exposure response analysis in the PopPK analysis.

5.2 Efficacy

The clinical documentation is based on one study with two phases.

The first phase involved a randomised, double-blind, placebo-controlled, parallel-group comparison of the 15 mg upadacitinib tablet with placebo over 14 weeks. The study medication could be administered in addition to any existing treatment with NSAIDs and/or cDMARDs and/or corticosteroids.
The patient selection and investigated endpoints were in line with the relevant guidelines and were similar to those used in the authorisation studies for TNF inhibitors, which are authorised for this indication. The primary endpoint was the ASAS 40 response rate in week 14. A statistically significant higher response rate for the primary endpoint was described for upadacitinib as compared to placebo in the first phase of the study.

Primary Endpoint: Analysis of ASAS40 at week 14 (NRI; FAS)

		Responder	Response Rate	Response Rate Diff (Upadacitinib - Placebo)		
Treatment	N	n (%)	(95% CI)[a]	Point Estimate	(95% CI)[b]	*P*-Value[c]
Placebo	94	24 (25.5)	25.5 (16.7, 34.3)			
Upadacitinib 15 mg QD	93	48 (51.6)	51.6 (41.5, 61.8)	26.1	(12.6, 39.5)	< 0.001

CI = confidence interval

a. 95% CIs for response rate are calculated based on normal approximation to the binomial distribution.

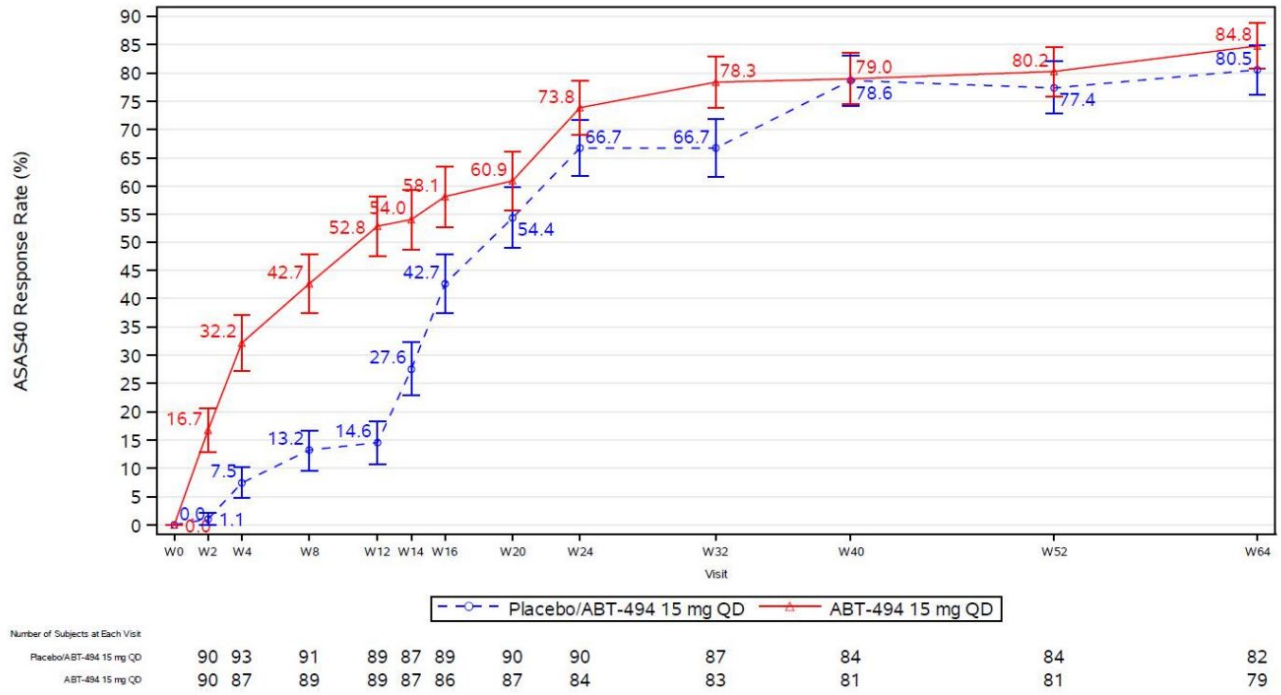
b. 95% CIs for response rate difference are calculated based on normal approximation using PROC FREQ.

c. Nominal *P*-value is constructed using Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor of screening hsCRP level.

Statistically significant benefits of upadacitinib also emerged for five of the 10 secondary endpoints controlled for multiple testing (including ASDAS and the radiographic endpoint SPARCC Score).

In the second phase of the study, which followed immediately after the first phase, an open-label treatment with upadacitinib was given for 90 weeks (either switching from placebo to upadacitinib or continuing upadacitinib, depending on the arm in the first phase of the study).
Efficacy data from the second phase with open-label treatment further support the efficacy of upadacitinib: The percentage of responders among patients receiving the initial placebo intervention increased after they switched to upadacitinib, whereas this percentage remained constant, with a low drop-out rate, among the patients who initially received the upadacitinib treatment.

ASAS40 Response Rate, Weeks 0 to 64 (AO, FAS)



5.3 Safety

In the study submitted for the indication of AS, 88 patients were exposed to upadacitinib for at least 3 months during the controlled phase, plus a total of 160 patients for 1 year or more during the open-label phase, corresponding to just under 240 patient years of exposure.
During the controlled study phase, AEs were described only slightly more frequently for upadacitinib compared to placebo, although suspected drug-related AEs were numerically more frequent. No deaths occurred and 1 SAE in each case for placebo and upadacitinib (myocardial infarction and spinal osteoarthritis) were observed. Nor were any deaths described in the long-term data. In line with the experience with RA, infections, gastrointestinal complications (but not perforations) and neutropenia were described.

5.4 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

In the submitted pivotal study, positive differences versus placebo are described for upadacitinib in AS in the investigated overall population regarding standard efficacy endpoints. The observed efficacy was similar to that reported for TNF inhibitors. The investigated population was heterogeneous in terms of previous medication and co-medication.
The benefit is offset by increased infections, episodes of lymphopenia and neutropenia, increased liver, lipid and creatinine phosphokinase levels, and a number of theoretical risks of adverse effects that are either rare or detected only after prolonged treatment.
Based on the reviewed documentation, Swissmedic considers the benefit-risk balance of upadacitinib to be positive when it is used as recommended for the treatment of ankylosing spondylitis (Bechterew's disease) in adult patients who had responded inadequately to previous treatment with non-steroidal anti-inflammatory drugs (NSAID).

5.5 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 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).

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/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 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 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 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 clinicial 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/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 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.

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

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 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/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.

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 ElViS (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)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	Primary Endpoint: • ACR50 at Week 12 Key Secondary Endpoints: • 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)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	Primary Endpoint: • ACR20 at Week 14 Key Secondary Endpoints: • 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:

	(661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• ACR20 at Week 12 Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤3.2) 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)	• Upadacitinib 15 mg • Placebo • Adalimumab 40 mg On background MTX	Primary Endpoint: • ACR20 at Week 12 Key Secondary Endpoints: • Clinical Remission (DAS28-CRP <2.6) at Week 12 • Low Disease Activity (DAS28-CRP ≤3.2) 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)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	Primary Endpoint: • ACR20 at Week 12 Key Secondary Endpoint: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • 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

[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

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 • Upadacitinib 30 mg • Placebo • Adalimumab 40 mg	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoints: • 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)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Primary Endpoint: • ACR20 at Week 12
			Key Secondary Endpoints: • 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 ≥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

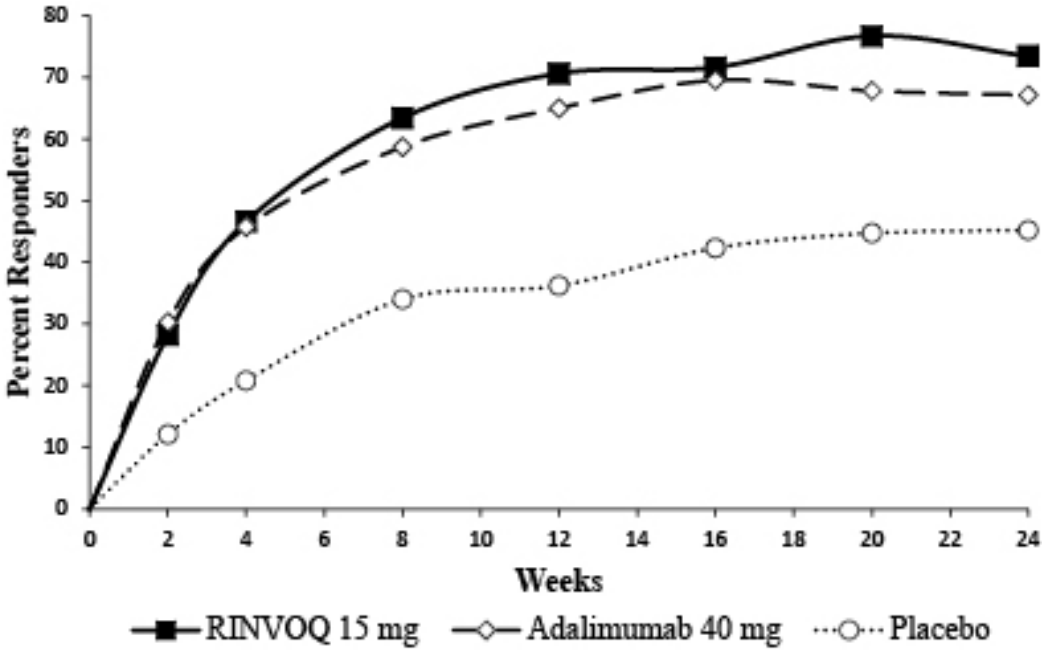

Table 9: Clinical response

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 • Placebo	Primary Endpoint: • ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASAS Partial Remission • BASDAI 50 • ASDAS-CRP • BASFI • SPARCC MRI score (spine) • ASQoL • BASMI • MASES • WPAI • 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

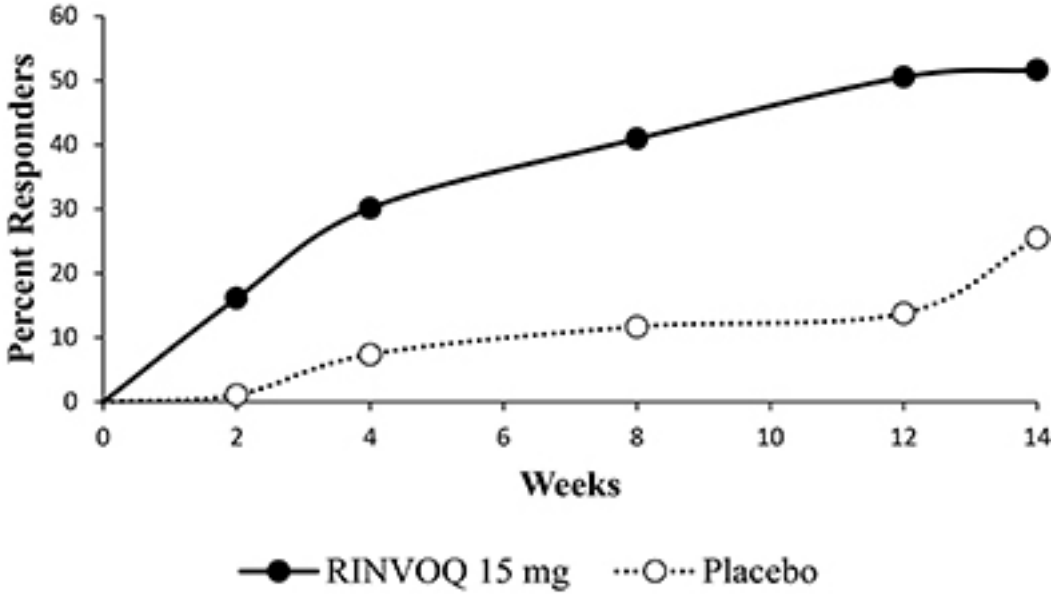

Table 13: Clinical Response in SELECT-AXIS 1

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.

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 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, 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