swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Rinvoq

International non-proprietary name: upadacitinib as upadacitinib hemihydrate
Pharmaceutical form: prolonged-release tablets
Dosage strength(s): 15 mg, 30 mg, 45 mg
Route(s) of administration: oral use
Marketing authorisation holder: AbbVie AG
Marketing authorisation no.: 67257
Decision and decision date: extension of therapeutic indication approved on 07.06.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AMS	Adapted Mayo score
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BIO-IR	Biologic therapy-intolerant or inadequate responder
CD	Crohn's disease
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
FACIT-F	Functional assessment of chronic illness therapy-fatigue
FDA	Food and Drug Administration (USA)
FMS	Full Mayo score
GCP	Good Clinical Practice
IBD	Inflammatory bowel disease
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ITT	Intention-to-treat
LoQ	List of Questions
MACE	Major adverse cardiac event
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NMSC	Non-melanoma skin cancer
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PK	Pharmacokinetics
PMS	Partial Mayo score
PopPK	Population pharmacokinetics
PY	Patient years
QD	Once daily (quaque die)
RBS	Rectal bleeding subscore
RESP_MAIN	Responders maintenance analysis set
RMP	Risk management plan
SFS	Stool frequency subscore
SwissPAR	Swiss Public Assessment Report
TNF	Tumour necrosis factor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UC	Ulcerative colitis
UPA	Upadacitinib

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

Rinvoq is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to at least 1 biologic agent, or for whom such a therapy is contraindicated.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Induction
The recommended induction dose of Rinvoq is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by Week 8, Rinvoq 45 mg once daily may be continued for an additional 8 weeks.
Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by Week 16.

Maintenance
The recommended maintenance dose of Rinvoq is 15 mg or 30 mg once daily based on individual patient presentation:

- A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment.
- A dose of 30 mg once daily may be appropriate for patients who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose for maintenance should be considered.
- For patients ≥ 65 years of age, the recommended maintenance dose is 15 mg once daily.
- In patients who have responded to treatment with Rinvoq, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	14 October 2022
Formal control completed	23 October 2022
List of Questions (LoQ)	25 April 2023
Response to LoQ	25 June 2023

Preliminary decision	1 September 2023
Response to preliminary decision	20 November 2023
2nd Preliminary decision	9 January 2024
Response to 2nd preliminary decision	10 March 2024
Labelling corrections	23 April 2024
Response to labelling corrections	13 May 2024
Final decision	7 June 2024
Decision	approval

3 Medical context

Ulcerative colitis (UC) is a life-long inflammatory bowel disease (IBD) of multifactorial aetiology with an abnormal mucosal immune response against commensal non-pathogenic bacteria of the colon, resulting in bowel inflammation. The age of onset varies from 15 to 40 years.

UC is characterised by recurrent episodes of mucosal inflammation of the colon, mainly involving the rectum and potentially progressing to the proximal colon. Symptoms related to the intestinal inflammation include diarrhoea with and without blood, increased frequency and reduced volumes of bowel movements, abdominal pain, urgency, and stool incontinence. Inflammation usually starts gradually and progresses over several weeks. Acute complications comprise severe bleeding, sometimes requiring colectomy, fulminant colitis with an increased risk for toxic megacolon, and perforation. Systemic manifestations comprise weight loss, muscle wasting, increased body temperature, and fatigue. Anaemia represents another frequent feature resulting from iron deficiency due to blood loss, anaemia of chronic disease, or autoimmune haemolytic anaemia. Over the course of the disease, up to 25% of UC patients develop extraintestinal features including arthritis, uveitis and episcleritis, erythema nodosum and pyoderma gangrenosum, primary sclerosing cholangitis, and autoimmune liver disease, an increased risk for venous and arterial thromboembolism, autoimmune haemolytic anaemia, and pulmonary complications.
Diagnosis of UC is based on:

- the presence of nonspecific features including chronic diarrhoea for more than 4 weeks
- active inflammation on endoscopy
- chronic changes on biopsy
- exclusion of alternative aetiologies for colitis such as Crohn's Disease (CD) or infection.

Endoscopy is used to determine the extent and severity of inflammation and to exclude involvement of the terminal ileum as a sign of CD. Nonspecific measurement of intestinal inflammation includes faecal calprotectin or lactoferrin.

Symptoms may be mild (defined as ≤ 4 stools/day ± blood) to severe (defined as > 10 stools/day, severe cramping and continuous bleeding). Disease severity is assessed by clinical disease activity scores such as the full, adapted, or partial Mayo score.

The majority of patients receive pharmacologic therapy, consisting typically of induction and maintenance phases depending on the severity and prognosis of the disease. The goal of therapy is the 'maintenance of remission', which is defined as glucocorticoid-free remission. Glucocorticoid-dependent UC corresponds to the impossibility to taper glucocorticoids to less than 10 mg per day within 3 months of starting therapy without disease recurrence or, if relapse occurs, within 3 months of stopping glucocorticoids. Conventional therapies such as topical or oral 5-aminosalicylates (mesalamine, olsalazine, sulfasalazine, balsalazide) are only sufficient in milder forms. Corticosteroids are used to induce rapid remission, particularly in moderate to severe UC. Due to side effects they have to be avoided in the long term. More recently, biologic agents administered intravenously (IV) or subcutaneously (SC) with different modes of action have been approved for the indication of moderate to severe ulcerative colitis.

Rinvoq (upadacitinib, UPA) is already approved in Switzerland for the following indications:

- Rheumatoid arthritis,
- Psoriatic arthritis,
- Ankylosing spondylitis (Bechterew's disease),
- Atopic dermatitis.

In parallel to the current UC submission, an application for an extension of the indication to include Crohn's disease (CD) was also submitted and assessed.

4 Nonclinical aspects

The nonclinical documentation submitted with the initial marketing authorisation application supports the approval for the addition of the new indication of ulcerative colitis for Rinvoq, prolonged-release tablets (upadacitinib).

No new nonclinical studies were conducted to support the requested extension of the indication. This was considered acceptable since, although a new dosage (45 mg) was requested for the treatment of ulcerative colitis, which was clinically evaluated, the higher dose of 45 mg does not change the safety profile, as the safety margins for the approved 15 mg dose were already low or non-existent.

The RMP adequately describes the results of the nonclinical studies and their relevance for the human use.

Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

From the nonclinical point of view, there are no objections to the approval of the requested extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

Pharmacokinetics
Upadacitinib PK and ADME properties were characterised as part of the initial application for the treatment of rheumatoid arthritis.

Sparse PK data were collected in UC patients from a Phase 2b study and a Phase 3 study and contributed to the population PK and exposure-response analyses.

Two population PK analyses were conducted to support the extension of indication for UC. The population PK model and the identified covariates for the rheumatoid arthritis population served as the basis for model development. The PK of upadacitinib was well described by a 2-compartment model with first-order absorption with lag time for the immediate-release formulation, mixed zero- and first-order absorption with lag time for the prolonged-release formulation and linear elimination. Overall, the upadacitinib PK in patients with UC was comparable with that in other patient populations. Furthermore, no differences between UC patients in the induction and the maintenance phases were observed. The population PK analyses indicated linear PK across the 7.5 mg to 45 mg prolonged-release dose range in UC subjects.
The final population PK model included the following statistically significant covariates: creatinine clearance, subject population, sex, and AST on CL/F, as well as sex and body weight on Vc/F. None of these covariates has a clinically relevant impact on the PK of upadacitinib. Overall, no dose adjustments are recommended based on sex, age, body weight, and race.

A dose reduction is recommended for UC patients with severe renal impairment, as well as for UC patients with mild and moderate hepatic impairment, i.e. 30 mg and 15 mg as induction and maintenance doses, respectively. Use in patients with end-stage renal disease is not recommended.

The DDI potential of upadacitinib was assessed as part of the initial application for the treatment of rheumatoid arthritis. A cocktail study was conducted to investigate the impact of 45 mg QD upadacitinib on CYP substrates. The findings were in line with previous studies, except that 45 mg dose is still considered to be a mild inhibitor of CYP2D6. For UC patients, a reduction of the induction and maintenance doses to 30 mg and 15 mg, respectively, is recommended when co-administered with a strong CYP3A4 inhibitor.
Based on the population PK analyses, the concomitant use of corticosteroids and aminosalicylates did not have an impact on upadacitinib exposures in subjects with UC.

Pharmacodynamics
As part of the initial application for the treatment of rheumatoid arthritis, the absence of QT interval prolongation for upadacitinib was demonstrated by exposure-response analyses using data from Phase 1 studies. Comparing the same exposure range of the previous QT exposure-response analyses and the C_{max} values for the proposed 45 mg QD dose in patients with UC and for the worst-case scenario estimated using the population PK model, it was shown that no QT prolongations are expected up to 2.1-fold the C_{max} following a 45 mg QD upadacitinib dose co-administered with a strong CYP3A inhibitor.

Using the data from the Phase 2b and 3 induction studies in subjects with UC, the relationships between upadacitinib plasma exposures and the clinical efficacy endpoints clinical remission, clinical response, endoscopic improvement, and endoscopic remission were investigated in subjects with UC at Week 8. A logistic regression model with a logarithmic shape function best described the exposure-response relationships for all evaluated efficacy endpoints, and they were all statistically significant. Overall, higher upadacitinib plasma exposures were associated with better efficacy for the clinical and endoscopic endpoints. However, it appears that the exposure-efficacy relationship approached a

plateau, and the improvement between the exposures reached with 30 mg and those reached with 45 mg was rather small.
Using the data from the Phase 3 maintenance study in subjects with UC, the relationships between upadacitinib plasma exposures and the clinical efficacy endpoints of clinical remission, endoscopic improvement, endoscopic remission, histologic-endoscopic mucosal improvement, and steroid-free clinical remission at Week 52 were investigated. A logistic regression model with a logarithmic shape function best described the exposure-response relationships for all evaluated efficacy endpoints except for endoscopic remission, and they were all statistically significant. Overall, higher upadacitinib plasma exposures were associated with better efficacy for the clinical and endoscopic endpoints. However, it appears that the exposure-efficacy relationship approached a plateau, and the improvement between the 15 mg and the 30 mg was rather limited. For endoscopic remission, only a treatment effect was observed.
None of the evaluated covariates had a clinically relevant impact on the exposure-response relationship for any of the clinical efficacy endpoints.

No statistically significant exposure-response relationship was observed for any of the investigated safety endpoints.

5.2 Dose finding and dose recommendation

The applicant conducted one Phase 2b dose finding study for the induction therapy in patients with moderately to severely active UC (M14-234 Substudy 1 (SS1)). The study consisted of 2 parts: ITT1A and ITT1B.

ITT1A (main subjects, actual dose-finding study)
Double-blind, randomised part evaluated 4 doses (7.5 mg, 15 mg, 30 mg, and 45 mg) upadacitinib (UPA) QD compared to placebo over 8 weeks. 250 subjects were randomised 1:1:1:1:1 to the 4 UPA doses and placebo. Randomisation was stratified by previous biologic therapy use (yes/no), baseline corticosteroid use (yes/no), and baseline adapted Mayo score (AMS) (≤7 or >7). 75% of the subjects enrolled in Substudy 1 were biologic therapy-intolerant or inadequate responders (Bio-IR), 25% of the subjects were Non-Bio-IR.

Primary endpoint:

- Proportion of subjects who achieve clinical remission per Adapted Mayo score (AMS) at Week 8 (defined as stool frequency subscore (SFS) ≤ 1, rectal bleeding subscore (RBS) of 0, and endoscopic subscore ≤ 1).

ITT1B (additional subjects)
132 additional subjects were enrolled in the 30 mg and 45 mg groups during the dose-selection analysis period of the ITT1A data to achieve a sufficient number of patients for the Phase 3 maintenance study. The results of these patients were not utilised for the dose-selection approach.

Results
In the ITT1A population, the primary and secondary endpoints were met in all dose groups, with the highest rates for the 45 mg dose, whereas in the ITT1B population the best results were observed with the 30 mg dose. Secondary endpoints and sensitivity analyses were in line with the results for the primary endpoint.

Subgroup analyses:
In most pre-defined subgroups, the results for the primary endpoint were consistent with the primary analysis, with the exception of non-White race, baseline AMS >7, and baseline FMS >9, possibly reflecting difficulties in inducing remission in patients with more active UC. In line with this hypothesis, participants who were Bio-IR achieved lower efficacy rates across all dose groups as compared to participants who were Non-Bio-IRs. Of note, secondary endpoints in the sub-groups (Bio-IR and non-Bio-IR) partially favoured lower doses:

- Clinical remission per AMS (defined as decrease from baseline in the AMS ≥2 points and ≥30% from baseline, PLUS a decrease in RBS ≥1 or an absolute RBS ≤1 at Week 8) was achieved in a higher proportion of subjects in the 15 mg subgroup than in the 30 mg UPA-treated Non-Bio-IR ITT1A subgroup.
- The same applies to endoscopic remission (defined as an endoscopic subscore of 0) for the Bio-IR ITT1A subgroup.
- Clinical remission per FMS (defined as FMS ≤2 with no subscore >1) was obtained in a numerically higher percentage of subjects in the 7.5 mg subgroup compared to the 30 mg UPA-treated BIO-IR subgroup, and in a higher percentage in the 15mg treated subgroup compared to the 30 mg UPA treated Non-Bio-IR subgroup.
- For the endpoint of clinical response per AMS at Week 8 (defined as decrease from baseline in the AMS ≥2 points and ≥30% from baseline, PLUS a decrease in RBS ≥1 or an absolute RBS ≤1), efficacy was better with the 15 mg dose compared to the 30 mg dose in Bio-IR subjects while, in the Non-Bio-IR subgroup, efficacy was better in the subjects treated with 30 mg compared to 45 mg.

There was a dose-dependent effect with respect to discontinuation rates (ITT1A: 7.5 mg: 4.3%, 15 mg: 8.2%, 30 mg: 11.5%, 45 mg: 10.7%, ITT1B: 30 mg: 4.6%, 45 mg: 6%), and the SAEs increased with the increasing dose administered.

Taking into consideration divergent results in Bio-IR regarding secondary endpoints, partially favouring lower doses and increasing rates of discontinuations and SAEs with higher doses, further justification for the proposed dose had to be provided. It was explained that the totality of data from Phase 1 and 2 studies (2a and 2b) were considered for dose selection. In addition, the results from the exposure-response analysis and multiple comparison procedure–modelling (MCP-Mod) were taken into consideration. Regarding the Phase 2b study, only the ITT1A (main study) population was included. This had been pre-specified in the clinical investigation plan and agreed with the regulators (EMA). The enrolment of additional patients in part B took place after part A was finished. Furthermore, the primary efficacy endpoint in ITT1A was in favour of the 45 mg dose. Similarly, the majority of secondary endpoints also supported the highest dose. The results of the subgroup analyses were not completely consistent with the main study results. However, the dosing groups were small with 50 patients planned per dosing cohort, which further limits the number of patients in the subgroups (Bio-IR and Non-Bio-IR). Thus, the interpretation of the results, in particular of the analysis of subgroups *Non-Bio-IR ITT1A* and *Bio-IR ITT1A,* was limited by small patient numbers. Additionally, the applicant highlighted that, in line with the findings from ITT1A, the exposure-response analyses showed statistically significant exposure-dependent increases in the percentages of subjects achieving clinical remission per AMS, clinical response per AMS, endoscopic improvement, and endoscopic remission at Week 8 over the exposure range associated with 7.5 mg to 45 mg QD. A lower dose of 30 mg QD was predicted to provide lower efficacy for both clinical and endoscopic endpoints by 4% to 7% compared to the 45 mg QD dose. Thus, the MCP-Mod method evaluating the primary endpoint of clinical remission per AMS at Week 8 in ITT1A also supported the dose selection of 45 mg among the 4 upadacitinib dose groups.
The overall approach of the dose selection and the pre-specification of study population (ITT1A) for the dose selection was endorsed. However, based on the Phase 2 study results and the small number of patients included per dosing group, the possibility that a lower induction dose than 45 mg would have provided comparable efficacy with fewer safety events cannot be completely excluded.

5.3 Efficacy

The applicant conducted 2 Phase 3 replicate studies investigating the efficacy and safety of the induction therapy (M14-234 Substudy 2 (SS2) and M14-675) and 1 Phase 3 study investigating the efficacy and safety of the maintenance therapy (M14-234 Substudy 3 (SS3)).

Induction therapy

Induction studies were conducted with the same design, endpoints, and patient populations (M14-234 SS2 and M14-675) in adult patients with moderate to severe UC, defined by an adapted Mayo score (AMS) of 5 to 9 points and an endoscopy subscore of 2 to 3, who had failed or not tolerated previous therapy. Both studies evaluated the efficacy and safety of oral 45 mg upadacitinib QD compared to placebo.

Primary endpoint:

- Proportion of subjects who achieve clinical remission per AMS at Week 8 (defined as SFS ≤1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤1)

Concomitant use of aminosalicylates, corticosteroids, and methotrexate was allowed. The studies consisted of 2 parts.

Part 1 (ITT1)
This part assessed 45 mg UPA vs. placebo over 8 weeks of double-blind treatment. Randomisation was 2:1 to UPA and placebo, respectively, and patients were stratified by:

- Bio-IR status (Bio-IR vs non-Bio-IR), and number of prior biologic treatments (≤1 or >1) for Bio-IR,
- corticosteroid use (yes or no) at baseline,
- AMS (≤7 or >7) at baseline
- within non-Bio-IR, the randomisation by previous biologic use (yes or no).

This part enrolled 473 subjects in study M14-234 SS2 (ITT1) and 515 subjects in study M14-675 (ITT1).

Part 2 / Extended induction phase (ITT2)
Subjects, who did not achieve a clinical response per AMS after 8 weeks of therapy with UPA could continue in Part 2 on 45 mg UPA for 8 weeks of open-label therapy.

Results
Of the enrolled 988 patients in ITT1 in both Phase 3 induction studies, the majority were male (62.3%) and White (67.2%). Mean age was 43.0 years. Nine patients were <18 years of age and 88 patients were 65 years of age and older. Mean disease duration was 8.017 years. Bio-IR patients constituted 51% (n=508) of the included population.
The enrolled population was heterogeneous regarding previous UC therapy, ranging from patients on their first conventional therapy to non-responders to biologics. Patients with previous JAK-inhibitor therapy were excluded from the pivotal studies to avoid confounding factors, which is reflected in the product information for healthcare professionals (“Clinical efficacy” section). In theory, a cumulative negative effect on safety upon switching from one to another JAK inhibitor cannot be excluded due to lack of data from randomised clinical trials (RCTs), and thus a contraindication was initially considered. However, this was not maintained since the practice of excluding patients with the same drug class is common in RCTs and does not lead to contraindications for other drugs. Furthermore, it can be anticipated that patients who do not respond to one JAK inhibitor may have very limited treatment options. Observational data submitted by the applicant in response to the preliminary decision suggested efficacy in patients who had been treated with another JAK inhibitor.

Both pivotal induction studies demonstrated significant treatment effects for UPA versus placebo for the primary clinical endpoint after 8 weeks of therapy (M14-234 SS2: 26.1% vs. 4.8% and M14-675: 33.5% vs. 4.1.%, respectively). The differences versus placebo regarding clinical remission per AMS were 21.6%, p<0.001 (M14-234 SS2) and 29.0%, p<0.001 (M14-675). Results for the secondary ranked endpoints and subgroup analysis were, overall, in agreement with the primary endpoint results.

In its **response to the LoQ**, the applicant performed additional sensitivity analyses excluding adolescents and patients with no documented failure of previous therapy. Analyses yielded similar

results. The Bio-IR sub-group had numerically lower responses to UPA compared to the biologic-naïve population. After 8 weeks of induction therapy, the differences between UPA 45 mg and placebo for the primary endpoint were 17.5% (M14-234 SS2) and 27.1% (M14-675). Detailed results for the Bio-IR population restricted to adult patients can be found in the information for healthcare professionals.

In total, 125 patients underwent open-label extended induction with UPA 45 mg, lasting a total of 16 weeks. After 16 weeks, 7 (5.6%) and 6 (4.9%) patients achieved clinical and endoscopic remission, respectively. Patients who achieved clinical response per AMS (n=60, 48%) were eligible for the maintenance study. Results remained similar for the adult population only (n=124), see information for healthcare professionals.

Maintenance therapy
The efficacy and safety of maintenance treatment for up to 52 weeks of exposure was investigated in M14-234 SS3. This study included all subjects who had achieved clinical response per AMS at the end of the induction Phase 2b (M14-234 SS1) and Phase 3 studies (M14-234 SS2 and M14-675). Clinical response was defined as:

- decrease from baseline in the AMS ≥2 points and ≥30% from baseline and
- decrease in RBS ≥1 or an absolute RBS ≤1

The maintenance therapy study consisted of 4 cohorts:

- Cohort 1: clinical responders to 8 weeks of UPA: 15 mg, 30 mg, and 45 mg QD
- Cohort 2: clinical responders to 8 weeks of placebo
- Cohort 3: clinical responders to 16 weeks of UPA 45 mg QD
- Cohort 4: clinical responders to 8 weeks of UPA 7.5 mg QD

Primary endpoint:
Proportion of subjects who achieve clinical remission per AMS (definition same as that in Substudy 2) at Week 52.
The primary analysis of the maintenance therapy was based on the first 450 patients included in cohort 1, who were 8-week-induction responders to 45 mg UPA QD enrolled under the 52-week protocol. They were re-randomised to the 2 maintenance doses (15 mg and 30 mg UPA QD) and placebo after the completion of Week 8 (ITT_A).

Results
In the primary analysis at Week 52, 42.3% and 51.7% of patients achieved clinical remission on 15 mg and 30 mg UPA dosing, respectively, as opposed to 12.1% of patients, who were switched to placebo. Differences versus placebo after 52 weeks of therapy amounted to 30.7% and 39.0% for 15 mg and 30 mg UPA dosing, respectively. Secondary multiplicity-controlled endpoints were also met. Detailed results for the primary and secondary ranked endpoints for Bio-IR adult population can be found in the information for healthcare professionals.

The results were numerically better for the higher maintenance dosing group. The sensitivity analysis performed for missing values due to COVID-19 and major protocol deviations were consistent with the primary analysis. In an additional sensitivity analysis excluding 6 adolescents and patients with no documented failure of previous therapy (n=6), the results were similar to the ITT_A analysis. Given that the primary analysis was not based on all 8-week induction responders included in the maintenance study, but on the subgroup of the first 450 8-week induction responders, the results for the remaining patients were requested to ensure the robustness of the results. In all 8-week induction responders (n=675), similar or higher response rates for UPA compared to the primary efficacy analysis were observed. In total, 40.4% and 53.6% of patients achieved clinical remission on 15 mg and 30 mg UPA doses, respectively, as opposed to 11.0 % of patients who were switched to placebo. Differences versus placebo after 52 weeks of therapy amounted to 29.8% and 42.6% for 15 mg and

30 mg UPA doses, respectively. Results for the secondary endpoints showed similar results. Numerically, the effect was higher with the UPA 30 mg maintenance dose for all secondary endpoints.

The results of the subgroup analysis were generally consistent with the primary analysis across all pre-specified subgroups. The Bio-IR subgroup (n=225, 49.9%) had numerically lower responses to UPA compared to the biologic-naïve population. After 52 weeks of therapy, 40.5% and 49.1% achieved clinical remission with 15 and 30 mg UPA QD, respectively. Although these response rates are numerically lower than in biologic-naïve patients (43.9 % and 54%), the differences versus placebo are higher (Bio-IR: 33.0 and 41.6 vs. Non-Bio-IR: 26.3 and 36.3%). The reason is the lower response to placebo in the Bio-IR group compared to the Non-Bio-IR group (7.5% vs. 17.6%). Analysis of the selected secondary endpoints in these subgroups yielded similar results. Some of the secondary endpoints did not differ or were better for the lower maintenance dose (15 mg) compared to the higher maintenance dose (30 mg). The post-hoc analysis provided with the response to the LoQ based on a larger sample size that included all enrolled 8-week induction responders Bio-IR under the 52-week protocol (n=332) yielded numerically better primary efficacy results for the higher UPA dose: 38.7% and 54.6% in the 15 mg and 30 mg groups respectively vs. 7.1% in the placebo group. Also, the majority of selected secondary endpoints were in favour of a higher maintenance dose (30 mg UPA).
In the extended induction group, continuation of the maintenance therapy resulted in clinical remission in 19% (4 out of 21, 15 mg QD) and 33.3% (8 out of 24, 30 mg QD) of patients after 52 weeks. Since this observation is based on a small population, there was uncertainty about the reproducibility of the effect. In a post-hoc analysis of all responders submitted, 9 patients out of 34 (26.5%) and 17 out of 39 (43.6%) were in clinical remission after 52 weeks of therapy. Secondary endpoints were consistent with the primary analysis. Overall, it appears to be a positive effect. However, the uncertainty about the reproducibility of the effect remains, as the studied group was small, and this is addressed in the information for healthcare professionals.

The number of patients ≥ 65 years was low. In total, 88 patients were included in the induction phase 3 studies. Of these, in the maintenance study ITT-A population, only 12, 13, and 15 patients were re-randomised to placebo, 15 mg UPA, and 30 mg UPA, respectively. The clinical remission rates after 52 weeks of therapy were numerically higher than in the population aged < 65 years (44.25 and 33.9% vs. 28.7% and 39.9% for 15 mg and 30 mg UPA dosing, respectively). This is further supported by the subgroup analysis according to median age showing better results in patients >42 years as opposed to patients ≤42 years. However, the small population of patients ≥65 years raised the uncertainty about the reproducibility of the effect **(LoQ).** In the **response to the LoQ**, all included patients ≥ 65 years were analysed (n=60). The primary endpoint and 8 out of 12 secondary endpoints favoured the lower maintenance dose in these patients. Overall results were numerically better compared with younger patients. In summary, favourable efficacy with the lower maintenance dose in the elderly was observed, although this was based on a small patient sample. Thus, the lower dose is also preferable in view of the higher possible adverse event rates as described below. This issue is addressed in the information for healthcare professionals.

5.4 Safety

The primary analysis of safety is based on the responders' maintenance set (RESP_MAIN). This set consists of:

- Safety Cohort 1: adult subjects who responded to UPA 45 mg 8-week induction treatment
- Safety Cohort 3: subjects who responded to UPA 45 mg 16-week induction treatment

Safety Cohort 1 reports data by randomised UPA maintenance dose and placebo. Data were censored at dose change. Of note, the placebo arm is a responder-withdrawal arm of patients exposed to 8 weeks of UPA induction therapy.

At the time of assessment, the primary safety analysis included:

- 285 subjects (413.8 patient years (PY)) who received at least 1 dose of UPA 15 mg QD as maintenance treatment (Cohort 1 and Cohort 3)
- 289 subjects (422.0 PY) who received at least 1 dose of UPA 30 mg QD as maintenance treatment (Cohort 1 and Cohort 3)
- 245 subjects (128.1 PY) who received at least 1 dose of placebo as maintenance treatment (Cohort 1) (N.B.: these patients were responders to 8-week UPA 45 mg QD induction therapy.)

It was based on the following exposures with constant UPA doses:

- 145 subjects completed 104 weeks (2 years) of UPA treatment,
- 21 subjects completed 156 weeks (3 years) of UPA treatment
- 7 patients completed 208 weeks (4 years) of UPA treatment

Higher rates of adverse events known for UPA from other indications were confirmed in the UC population: MACE, venous thromboembolism, pulmonary embolism, haematological abnormalities (neutropenia, lymphopenia), infections (serious infections, tuberculosis, herpes zoster, opportunistic infections), hepatic disorders, gastrointestinal perforations, cholesterol, creatinine and CPK increases. Furthermore, there was a trend towards reduced pulse rate and increased weight. Other, more frequent, AEs in the UPA group included acne, folliculitis, hyperlipidaemia, rash and hypertension. Since most of the AEs of special interest were dose dependent, there was a concern that patients undergoing extended induction (16-weeks) have a higher risk of adverse events. A submitted supplementary comparative analysis of 16-week induction responders and 8-week responders did not reveal any significant imbalances. However, given the small number of patients and related exposures (PY=38.9), the higher risk of adverse events with longer exposition cannot be completely excluded, and this is addressed in the information for healthcare professionals.

Since the overall number of elderly patients included in the Phase 3 programme was low, the analysis of AEs is limited. There is, however, a trend for higher rates of AEs in this group, and this is addressed in the information for healthcare professionals.

There is a class safety signal for JAK inhibitors due to observations of higher rates of deaths, malignancies and MACE compared to TNF inhibitors in the ORAL Surveillance Study. This study was appropriately designed to investigate differences in deaths, MACE and malignancies. The higher risk with separation of the Kaplan-Mayer curves for the pre-defined adverse events was detectable after 40 months of therapy. This raised uncertainty regarding the long-term safety of UPA as the primary safety analysis included only 21 patients exposed to 36 months of UPA therapy. Furthermore, the safety set chosen by the applicant for the primary analysis (RESP_MAIN) is based on the subgroup that includes only responders to UPA 8-week induction therapy 45 mg QD until dose switching. This set is incomplete as it does not include patients who were non-responders in the induction studies. Nor does it include AEs of patients after switching to a higher dose. Moreover, the placebo cohort in the primary analysis (RESP_MAIN) is actually a responder-withdrawal cohort, which includes 8-week responders to 45 mg UPA QD, who were re-randomised to placebo. Thus, adverse events with a causal relationship to UPA and a longer incubation period than 8 weeks are potentially captured here. An additional supplementary analysis was submitted, with adverse events in all placebo-treated patients until the switch to UPA (“pure” placebo group), and AEs in patients after any UPA exposure (any UPA group). In these analyses, the % of patients, who died was equal in both groups (0.3%; 4 patients and 1 patient in the Any UPA and “pure” placebo groups, respectively). Overall, 40 events of possible malignancy in 32 patients in the Any UPA group were detected, as opposed to 1 event in the “pure” placebo group. A total of 36 malignancies were diagnosed in 28 Any UPA patients vs. 0 events in the “pure” placebo group. Of the malignancies in the Any UPA group, 20 cases were non-melanoma skin cancer (NMSC) and 16 cases were non-NMSC tumours. There was no clear pattern of non-NMSC malignancies. The percentages of patients with malignancies and Event Rate/100 PYs in any UPA were as follows:

- Potential malignancies: 2.5%, 1.6

- Malignancy: 2.2%, 1.4
- Non NMSC malignancy: 1.2%, 0.6
- NMSC malignancy: 1.2%, 0.8

5.5 Final clinical benefit-risk assessment

The current application concerns an extension of the indication for Rinvoq to include treatment of patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. UC is characterised by recurrent episodes of mucosal inflammation of the colon, mainly involving the rectum and potentially progressing to the proximal colon. Symptoms related to the intestinal inflammation include diarrhoea with and without blood, increased frequency and reduced volumes of bowel movements, abdominal pain, urgency, and stool incontinence. Treatment for moderately to severely active UC consists mainly of conventional therapy with mesalazine (5-ASA), corticosteroids and immunosuppressive biologic drugs. Of them most commonly used are TNF inhibitors. Rinvoq is the second JAKi, approved for ulcerative colitis (UC).
The efficacy was demonstrated in the primary efficacy analysis of the first 450 8-week induction responders and confirmed in the analysis of all 8-week induction responders. The results for the secondary endpoints, sensitivity analyses and subgroup analyses were consistent with the primary results. In particular, a positive effect was shown in adult patients with an inadequate response or intolerance to biologic treatment (Bio-IR). There is an ongoing safety concern regarding JAK inhibitors, including UPA, with respect to an increased risk of MACE, malignancies, and all-cause mortality. The current submission confirmed this concern, with the higher occurrence of adverse events of special interest (AESI) in the active group upon relatively short exposure. Of these, serious AEs such as malignancies occurred only in UPA-exposed patients. A pooled analysis of UC and CD (Crohn's disease) further confirmed this pattern. The post-hoc analysis of risk factors as well as an indirect meta-analysis of available biologic therapies provided by the applicant cannot eliminate safety concerns, as these analyses are subject to significant design constraints and require confirmation in well-designed, head-to-head RCTs. Taking into account a more favourable safety profile for other biologic treatments such as TNF inhibitors, the benefit-risk assessment is considered positive only in patients who failed their first biologic treatment. The lower maintenance dose is preferred unless efficacy cannot be achieved.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for 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 valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure that the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

IMPORTANT WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCIES, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

- **Increased risk** of **serious** bacterial, fungal, viral, and opportunistic **infections** leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with RINVOQ if a serious infection occurs until the infection is controlled.
- **Higher rate of all-cause mortality,** including sudden cardiovascular death with another Janus kinase (JAK) inhibitor compared with Tumour Necrosis Factor (TNF) blockers in rheumatoid arthritis (RA) patients.
- **Malignancies** have occurred in patients treated with RINVOQ. Higher rates of **lymphoma and lung cancer** with another JAK-Inhibitor compared with TNF blockers in RA patients.
- **Higher rate of MACE** (defined as **cardiovascular death, myocardial infarction, and stroke)** with another JAK inhibitor compared with TNF blockers in RA patients.
- **Thromboembolic events** have occurred in patients treated with RINVOQ. Increased incidence of **pulmonary embolism, venous** and **arterial thrombosis** with another JAK inhibitor compared with TNF blockers.

For further information, please read the "Warnings and Precautions" section.

RINVOQ®

Composition

Active substances

Upadacitinib as upadacitinib hemihydrate

Excipients

Microcrystalline cellulose, hypromellose, mannitol (E421), tartaric acid, silica (colloidal anhydrous), magnesium stearate, polyvinyl alcohol, macrogol 3350, talc, titanium dioxide (E171), black iron oxide (E172) (15 mg strength only), iron oxide red (E172) , iron oxide yellow (E172) (45 mg strength only).

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.

RINVOQ 30 mg prolonged-release tablets

Red oblong biconvex prolonged-release tablets imprinted on one side with ‘a30’.
Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 30 mg of upadacitinib.

RINVOQ 45 mg prolonged-release tablets

Yellow oblong biconvex prolonged-release tablets imprinted on one side with ‘a45’.
Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 45 mg of upadacitinib.

Indications/Uses

Rheumatoid Arthritis

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

Psoriatic Arthritis

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

Ankylosing Spondylitis

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

Atopic Dermatitis

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

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to at least one biologic agent, or for whom such a therapy is contraindicated.

Crohn's Disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to at least one biologic agent, or for whom such a therapy is contraindicated.

Dosage/Administration

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

Rheumatoid Arthritis

The recommended dose of RINVOQ is 15 mg once daily.

Psoriatic Arthritis

The recommended dose of RINVOQ is 15 mg once daily.

Ankylosing Spondylitis

The recommended dose of RINVOQ is 15 mg once daily.

Atopic Dermatitis

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

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

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

Ulcerative Colitis

Induction

- The recommended induction dose of RINVOQ is 45 mg once daily for 8 weeks.
- In patients who do not show adequate therapeutic benefit by Week 8, the use of RINVOQ 45 mg once daily for an additional 8 weeks can be considered (see Properties and Effects section), taking into account the patients' risk of MACE, VTE and malignancies.

- There are no data to support the benefit of induction treatment beyond 16 weeks. RINVOQ should be discontinued permanently in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance (for patients with clinical response after 8 or 16 weeks of induction)

- The recommended maintenance dose of RINVOQ is 15 mg or 30 mg once daily.
- A dose of 30 mg may be considered in patients with high disease activity or who have required 16-week induction treatment or who did not respond adequately to 15 mg once daily (see Properties and Effects section), taking into account the patients' risk of MACE, VTE and malignancies (see Warnings and Precautions section).
- The lowest effective maintenance dose should always be used.
- For patients ≥ 65 years of age, the recommended maintenance dose is 15 mg once daily.
- In patients who have responded to treatment with RINVOQ, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

For dose adjustments with concomitant strong cytochrome P450 (CYP) 3A4 inhibitors, see "Interactions."

Crohn's Disease

Induction

- The recommended induction dose of RINVOQ is 45 mg once daily for 12 weeks.
- In patients who do not achieve adequate therapeutic benefit by Week 12, extended induction for an additional 12 weeks with a dose of 30 mg once daily can be considered (see Properties and Effects section), taking into account the patients' risk of MACE, VTE and malignancies.
- RINVOQ should be discontinued permanently in any patient who shows no evidence of therapeutic benefit after a total of 24 weeks of treatment.

Maintenance (for patients with clinical response after 12 or 24 weeks of induction)

- The recommended maintenance dose of RINVOQ is 15 mg or 30 mg once daily.
- A dose of 30 mg may be considered in patients with high disease activity or who have required 24-week induction treatment or who do not respond adequately to 15 mg once daily (see Properties and Effects section), taking into account the patients' risk of MACE, VTE and malignancies (see Warnings and Precautions section).
- The lowest effective maintenance dose should always be used.
- For patients ≥ 65 years of age, the recommended maintenance dose is 15 mg once daily.

For dose adjustments with concomitant strong CYP3A4 inhibitors, see "Interactions".

In patients who are responding to induction or maintenance treatment with RINVOQ, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Interactions

For patients with ulcerative colitis and Crohn's disease receiving strong inhibitors of CYP3A4 (e.g., ketoconazole, clarithromycin), the recommended induction dose is 30 mg once daily and the recommended maintenance dose is 15 mg once daily (see Interactions).

Administration

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

Dose initiation

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

Dose interruption

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

Table 1: Recommended Dose Interruption for Laboratory Abnormalities

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

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.

Immunosuppressive medicinal products

Combination with other potent immunosuppressants such as azathioprine, 6-mercaptopurine and 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

RINVOQ is not recommended for use in patients with severe hepatic impairment (Child Pugh C) (see «Pharmacokinetics»).

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Atopic Dermatitis:
No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

Ulcerative Colitis and Crohn's disease:
For patients with mild to moderate hepatic impairment (Child-Pugh A or B) the recommended dosage is:

- Induction: 30 mg once daily
- Maintenance: 15 mg once daily

Patients with impaired renal function

No dose adjustment is required in patients with mild or moderate 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) and is therefore not recommended for use in these patients.

For patients with severe renal impairment, the following doses are recommended:

Table 2. Recommended dose for Severe Renal Impairment[a]

Indication	**Recommended once daily dose**

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis	15 mg
Ulcerative Colitis and Crohn's disease	Induction: 30 mg
	Maintenance: 15 mg
[a]estimated glomerular filtration rate (eGFR) 15 to < 30 ml/min/1.73m^2	

Elderly patients

There are limited data in patients aged 75 years and older. There was a higher rate of overall adverse events, including serious infections, in patients 65 years and older.
For ulcerative colitis and Crohn's disease, doses higher than 15 mg once daily for maintenance therapy are not recommended in patients aged 65 years and older (see «Undesirable effects»).

Children and adolescents

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

Contraindications

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

Warnings and precautions

Use in patients aged 65 years and older
Considering the increased risk of severe infections, myocardial infarction, and malignancies in connection with JAK-inhibitors in patients over 65 years of age, RINVOQ should be used with particular caution in patients with ulcerative colitis or Crohn's disease in this age group and should only be used if no suitable treatment alternatives are available in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or atopic dermatitis in this age group (see further details in "Warnings and precautions").
There is an increased risk of adverse reactions with the upadacitinib dose of 30 mg once daily in patients aged 65 years and older. The recommended dose for long-term use is 15 mg once daily for this patient population.

Extended induction for ulcerative colitis
Data for patients with extended induction (16 weeks) are limited. An increased risk of adverse events cannot be excluded for those patients.

Serious infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ are pneumonia, cellulitis, and urinary tract infections (see «Undesirable effects»). Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis and cryptococcosis were reported with RINVOQ. A higher rate of serious infections was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

Avoid use of RINVOQ in patients with an active, serious infection, including localized infections.

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

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

  or

- with underlying conditions that may predispose them to infection.

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

Tuberculosis

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

Viral reactivation

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

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

All-cause mortality
In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with Tumour Necrosis Factor (TNF) inhibitors. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

Malignancy
Malignancies, including lymphomas, were observed in clinical studies of RINVOQ (see «Undesirable effects»). A higher rate of malignancies, driven by NMSC, was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.
In a large randomized post-marketing safety study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of malignancy,

particularly lung cancer, lymphomas and non-melanoma skin cancer [NMSC], was observed with a different JAK inhibitor compared to TNF blockers.

In this study, patients over 65 years of age and patients who were current or past smokers had an additionally increased risk of malignancies.

RINVOQ should be used with particular caution in patients with ulcerative colitis or Crohn's disease and should only be used if no suitable treatment alternatives are available in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or atopic dermatitis for:

- patients over 65 years of age,
- patients who are current or past smokers,
- patients with other risk factors for malignant diseases (e.g. current malignant disease or a history of malignant disease other than a successfully treated non-melanoma skin cancer).

Non-Melanoma Skin Cancer (NMSC)
NMSCs have been reported in patients treated with RINVOQ. In a large randomized post-marketing safety study in rheumatoid arthritis patients 50 years and older with at least one cardiovascular risk factor, an increase in NMSC-cases, including squamous-cell carcinomas of the skin, was observed with a different JAK inhibitor compared to TNF blockers. Since the incidence of NMSC is increased in elderly patients and patients with history of NMSC, these patients should be treated with caution. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see "Undersirable effects").

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. In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased and dose-dependent incidence of thromboembolic events (including pulmonary embolism) was observed in patients treated with a different JAK inhibitor compared to patients receiving TNF blockers. The majority of these events were serious and some resulted in death.

Prescribing physicians should evaluate regularly risk factors for thromboembolic events of patients before starting treatment and during treatment. Promptly examine patients with signs and symptoms of thromboembolic events and discontinue treatment with RINVOQ in patients with suspected thromboembolic events, regardless of dose or indication.

Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy (see Undesirable effects).

Embryo-Fetal Toxicity

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

Gastrointestinal perforations

Gastrointestinal perforations were rarely observed under the treatment with RINVOQ. Events of gastrointestinal perforations have been reported in clinical trials and from post-marketing sources. RINVOQ should be used with caution in patients who may be at risk for gastrointestinal perforation (e.g., patients with diverticular disease, a history of diverticulitis, or who are taking nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or opioids). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

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»).

Major adverse cardiovascular events (MACE)

In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of MACE (defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke), was observed with a different JAK inhibitor compared with TNF blockers. In this study, patients over 65 years of age,

patients who were current or past smokers, and patients with cardiovascular risk factors had an additional increased risk of MACE.

RINVOQ should be used with particular caution in patients with ulcerative colitis or Crohn's disease and should only be used if no suitable treatment alternatives are available in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or atopic dermatitis for:

- patients over 65 years of age,
- patients who are current or past smokers,
- patients with other cardiovascular risk factors.

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.

Medication Residue in Stool
Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

Interactions

Potential for other medicinal products to affect the pharmacokinetics of upadacitinib

Upadacitinib is metabolized in vitro by CYP3A4 with a minor contribution from CYP2D6.

Strong CYP3A4 inhibitors
Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, and grapefruit). RINVOQ 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. For patients with inflammatory bowel diseases using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily and the recommended maintenance dose is 15 mg once daily (see “Dosage/Administration”). Alternatives to strong CYP3A4 inhibitor medications should be considered when used in the long-term. Food or drink containing grapefruit should be avoided during treatment with upadacitinib.

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 3.

Table 3. 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**

Methotrexate	10 to 25 mg/week for at least 4 weeks	6, 12 or 24 mg twice dailyb x 26 days	10	0.97 (0.86-1.09)	0.99 (0.93-1.06)	No dose adjustment
Strong CYP3A4 inhibitor: Ketoconazole	400 mg once daily x 6 days	3 mg single dose [b]	11	1.70 (1.55-1.89)	1.75 (1.62-1.88)	RINVOQ 15 mg once daily is the recommended dose for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. Use with caution if used chronically. For ulcerative colitis and Crohn's disease, the induction dose should be reduced to 30 mg and the maintenance dose should be reduced to 15 mg when combined with strong CYP3A4 inhibitors. Alternatives to strong CYP3A4 inhibitor medications should be considered when used in the long-term.
Strong CYP3A4 inducer: 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

OATP1B inhibitor: Rifampicin	600 mg single dose	12 mg single dose[b]	12	1.14 (1.02-1.28)	1.07 (1.01-1.14)	No dose adjustment is recommended when upadacitinib is administered with OATP1B inhibitors

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

In vitro studies indicate that upadacitinib does not inhibit the activity of cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at clinically relevant concentrations. *In vitro* studies indicate that upadacitinib induces CYP3A4 but does not induce CYP2B6 or CYP1A2 at clinically relevant concentrations. *In vitro* studies indicate that upadacitinib does not inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations.

Clinical studies indicate that upadacitinib has no clinically relevant effects on the pharmacokinetics of co-administered drugs. Following upadacitinib 30 mg and 45 mg once daily, the effects on each CYP enzymes (CYP1A2, CYP3A, CYP2C9, and CYP2C19) were similar between two doses except for the effect on CYP2D6. Following upadacitinib 30 mg and 45 mg once daily, a weak induction of CYP3A4 was observed. A weak inhibition of CYP2D6 was observed at upadacitinib 45 mg but not at 30 mg.

The effect of upadacitinib on plasma exposures of other drugs is provided in Table 4.

Table 4. 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**
Methotrexate	10 to 25 mg/week for at least 4 weeks	6, 12 or 24 mg twice daily[b] x 26 days	10	1.03 (0.86-1.23)	1.14 (0.91-1.43	No dose adjustment
Sensitive CYP1A2 Substrate: Caffeine	200 mg single dose	45 mg once daily[c] x 11 days	18	1.05 (0.97-1.14)	1.04 (0.95-1.13)	No dose adjustment
Sensitive CYP3A Substrate: Midazolam	5 mg single dose	30 mg once daily[c] x 10 days	20	0.74 (0.68-0.80)	0.74 (0.68-0.80)	No dose adjustment
Sensitive CYP3A Substrate: Midazolam	5 mg single dose	45 mg once daily[c] x 10 days	19	0.75 (0.69-0.83)	0.76 (0.69-0.83)	No dose adjustment
Sensitive CYP2D6 Substrate: Dextromethorphan	30 mg single dose	30 mg once daily[c] x 11 days	20	1.09 (0.98-1.21)	1.07 (0.95-1.22)	No dose adjustment
Sensitive CYP2D6 Substrate: Dextromethorphan	30 mg single dose	45 mg once daily[c] x 11 days	19	1.30 (1.13- 1.50)	1.35 (1.18- 1.54)	No dose adjustment
Sensitive CYP2C9 Substrate: S-Warfarin	10 mg single dose	45 mg once daily[c] x 11 days	18	1.18 (1.05-1.33)	1.12 (1.05-1.20)	No dose adjustment

				Ratio (90% CI)[a]		
Co-administered Drug	**Regimen of Co-administered Drug**	**Regimen of Upadacitinib**	**N**	**C_{max}**	**AUC**	**Clinical Impact**
Sensitive CYP2C19 Marker: 5-OH Omeprazole to Omeprazole metabolic ratio	40 mg single dose of omeprazole	45 mg once daily[c] x 11 days	18	--	0.96 (0.90-1.02)	No dose adjustment
CYP2B6 Substrate: Bupropion	150 mg single dose	30 mg once daily[c] x 11 days	22	0.87 (0.79-0.96)	0.92 (0.87-0.98)	No dose adjustment
Rosuvastatin	5 mg single dose	30 mg once daily[c] 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[c] x 10 days	24	0.88 (0.79-0.97)	0.77 (0.70-0.85)	No dose adjustment
Oral Contraceptive: Ethinylestradiol	0.03 mg single dose	30 mg once daily[c] x 14 days	22	0.96 (0.89-1.02)	1.11 (1.04-1.19)	No dose adjustment
Oral Contraceptive: Levonorgestrel	0.15 mg single dose	30 mg once daily[c] x 14 days	22	0.96 (0.87-1.06)	0.96 (0.85-1.07)	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.

[b] Immediate-release formulation

[c] Extended-release formulation

No dose adjustment is recommended for CYP3A substrates, CYP2D6 substrates, rosuvastatin or atorvastatin when coadministered with upadacitinib. Upadacitinib has no relevant effects on plasma exposures of ethinylestradiol, levonorgestrel, methotrexate, or medicinal products that are substrates for metabolism by CYP1A2, CYP2B6, 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

In the placebo-controlled clinical trials for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, the most commonly reported adverse drug reactions (ADRs) occurring in ≥2% of patients treated with RINVOQ 15 mg were upper respiratory tract infections, blood creatine phosphokinase (CPK) increased, alanine transaminase increased, bronchitis, nausea, neutropenia, cough, aspartate transaminase increased, and hypercholesterolemia.

In the placebo-controlled atopic dermatitis clinical trials, the most commonly reported adverse drug reactions (≥2% of patients) with RINVOQ 15 mg were upper respiratory tract infection, acne, herpes simplex, headache, blood CPK increased, cough, folliculitis, abdominal pain, nausea, and influenza.

In the placebo-controlled ulcerative colitis and Crohn's disease induction and maintenance clinical trials, the most commonly reported adverse reactions (≥3% of patients) with RINVOQ 45 mg, 30 mg or 15 mg were upper respiratory tract infection, pyrexia, blood CPK increased, anemia, headache, acne, herpes zoster, neutropenia, rash, pneumonia, hypercholesterolemia, bronchitis, aspartate transaminase increased, fatigue, folliculitis, alanine transaminase increased, herpes simplex, and influenza.

The most common serious adverse reactions were serious infections (see "warnings and precautions").

Rheumatoid Arthritis
A total of 4443 patients with rheumatoid arthritis were treated with RINVOQ 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 RINVOQ in clinical studies representing 1639.2 patient-years of exposure, of whom 722 were exposed to RINVOQ 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 596 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the two clinical studies representing 577.3 patient-years of exposure, of whom 228 were exposed to RINVOQ 15 mg for at least one year.

Atopic Dermatitis

A total of 2898 patients with atopic dermatitis were treated with RINVOQ in clinical studies representing approximately 3255 patient-years of exposure, of whom 1920 patients were exposed for at least one year. In the three global Phase 3 studies, 1239 patients received at least 1 dose of RINVOQ 15 mg, of whom 791 were exposed for at least one year.

Four global placebo-controlled studies (one Phase 2 study and three Phase 3 studies) were integrated (899 patients on RINVOQ 15 mg once daily and 902 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 16 weeks after treatment initiation.

Ulcerative Colitis

RINVOQ has been studied in patients with moderately to severely active UC in one Phase 2b and three Phase 3 (UC-1, UC-2 and UC-3) randomized, double-blind, placebo-controlled clinical studies and a long-term extension study (see «Clinical Efficacy») with a total of 1304 patients representing 1821 patient-years of exposure, of whom 721 patients were exposed for at least one year.

In the induction studies (Phase 2b, UC-1, and UC-2), 719 patients received at least 1 dose of RINVOQ 45 mg, of whom 513 were exposed for 8 weeks and 127 subjects were exposed for up to 16 weeks.

In the maintenance study UC-3 and the long-term extension study, 285 patients received at least one dose of RINVOQ 15 mg, of whom 131 were exposed for at least one year, and 291 patients received at least one dose of RINVOQ 30 mg, of whom 137 were exposed for at least one year.

Crohn's disease

RINVOQ has been studied in patients with moderately to severely active CD in three Phase 3 (CD-1, CD-2, and CD-3) randomized, double-blind, placebo-controlled clinical studies (see CLINICAL STUDIES) with a total of 833 patients representing 1203 patient-years of exposure, of whom a total of 536 patients were exposed for at least one year.

In the induction studies (CD-1 and CD-2), 674 patients received at least one dose of RINVOQ 45 mg during the placebo-controlled period, of whom 592 were exposed for 12 weeks and 142 patients received at least one dose of RINVOQ 30 mg during the extended treatment period.

In the maintenance study CD-3, 221 patients received at least one dose of RINVOQ 15 mg, of whom 89 were exposed for at least one year and 229 patients received at least one dose of RINVOQ 30 mg, of whom 107 were exposed 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).
The frequencies are based on the highest of the rates of adverse reactions reported with RINVOQ in clinical trials in one or more indications (rheumatologic disease (15 mg), atopic dermatitis (15 mg and 30 mg), ulcerative colitis (15 mg, 30 mg and 45 mg) or Crohn's disease (15 mg, 30 mg, and 45 mg)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. When notable differences in frequency were observed between indications, these are presented in the footnotes below.

Infections and infestations
Very Common: Upper respiratory tract infections (URTI)[a] (22.6% for 15 mg and 25.4% for 30 mg in atopic dermatitis trials)
Common: Bronchitis[b,c], Herpes zoster[d], Herpes simplex[e], Folliculitis, Influenza, Pneumonia[f,g], Urinary tract infection
Uncommon: Oral candidiasis

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Non-melanoma skin cancer[c,h,i]

Blood and lymphatic system disorders
Common: Neutropenia[j], Anemia, Lymphopenia[k]

Metabolism and nutrition disorders
Common: Hypercholesterolemia[c,l], Hyperlipidemia[m], weight increased[h]
Uncommon: Hypertriglyceridemia

Nervous system disorders
Common: Headache[n]

Respiratory, thoracic and mediastinal disorders
Common: Cough

Gastrointestinal disorders
Common: Nausea, Abdominal pain[o]
Uncommon: Gastrointestinal perforation[p]

Hepatobiliary disorders
Common: ALT increased[c], AST increased[c]

Skin and subcutaneous tissue disorders
Very Common: Acne[h,q,r,s] (9.6% for 15 mg and 15.1% for 30 mg in atopic dermatitis trials)
Common: Urticaria[h,r], Rash[t]

Musculoskeletal and connective tissue disorders
Common: Blood creatine phosphokinase (CPK) increased

General disorders
Common: Pyrexia, Fatigue

[a] URTI includes acute sinusitis, laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, and viral upper respiratory tract infection
[b] Bronchitis includes bronchitis, bronchitis bacterial, bronchitis viral, and tracheobronchitis
[c] In atopic dermatitis trials, the frequency of bronchitis, non-melanoma skin cancer, hypercholesterolemia, ALT increased, and AST increased was uncommon.
[d] Herpes zoster includes herpes zoster, herpes zoster disseminated, herpes zoster meningitis, post herpetic neuralgia, and varicella zoster virus infection
[e] Herpes simplex includes genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes simplex pharyngitis, herpes virus infection, nasal herpes, ophthalmic herpes simplex, and oral herpes
[f] Pneumonia includes atypical pneumonia, COVID-19 pneumonia, pneumonia, pneumonia bacterial, pneumonia pneumococcal, and pneumonia viral
[g] Pneumonia was common in Crohn’s disease and uncommon across other indications.
[h] In Crohn’s disease trials, the frequency was common for acne, and uncommon for urticaria, weight increased, and non-melanoma skin cancer.
[i] Non-melanoma skin cancer includes basal cell carcinoma
[j] Neutropenia includes granulocyte count decreased, neutropenia, and neutrophil count decreased
[k] Lymphopenia incudes lymphocyte count decreased, lymphocyte percentage decreased, and lymphopenia
[l] Hypercholesterolemia includes blood cholesterol increased and hypercholesterolemia
[m] Hyperlipidemia includes dyslipidemia, hyperlipidemia, and low density lipoprotein increased
[n] Headache includes headache, sinus headache, and tension headache

[o] Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain

[p] Frequency is based on Crohn's disease clinical trials.

[q] Acne includes acne, acne cystic, and dermatitis acneiform

[r] In rheumatologic disease trials, the frequency was common for acne and uncommon for urticaria.

[s] In ulcerative colitis trials, the frequency was common for acne.

[t] Rash includes rash, rash erythematous, rash follicular, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash generalized

Rheumatoid Arthritis

Specific Adverse Reactions

Infections

In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg group was 27.4% compared to 20.9% in the placebo group. In MTX-controlled studies, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group The overall long-term rate of infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies (2630 patients) was 93.7 events per 100 patient-years.

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

Tuberculosis

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

Opportunistic Infections (excluding tuberculosis)

In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the RINVOQ 15 mg group was 0.5% compared to 0.3% in the placebo group. In MTX-controlled studies, there were no cases of opportunistic infection over 12/14 weeks in

the RINVOQ 15 mg monotherapy group and 0.2% in the MTX group. The overall long-term rate of opportunistic infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.6 events per 100 patient-years.

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

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.

Non-Melanoma Skin Cancer (NMSC)

In placebo-controlled clinical studies, the frequency of NMSC over 12/14 weeks in the RINVOQ 15 mg group and placebo group was 0% and <0.1%, respectively. The long-term rate of NMSC for all patients treated with RINVOQ 15 mg in the clinical trial program was 0.3 per 100 patient-years.

Gastrointestinal Perforations

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

Thrombosis

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

Hepatic transaminase elevations

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

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

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

Lipid elevations

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

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

Creatine phosphokinase (CPK)

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

Neutropenia

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

neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

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

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

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

Atopic dermatitis

Opportunistic infections (excluding tuberculosis)

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

Ulcerative Colitis

Specific Adverse Reactions

For all of the following adverse reaction rates, patients in the placebo group and the RINVOQ 15 mg and 30 mg groups referenced in the placebo-controlled maintenance study all received RINVOQ 45 mg for 8 weeks prior to entering the placebo-controlled maintenance study.

Infections
In the placebo-controlled induction studies, the frequency of infection over 8 weeks in the RINVOQ 45 mg group and the placebo group was 20.7% and 17.5%, respectively. In the placebo-controlled

maintenance study, the frequency of infection up to 52 weeks in the RINVOQ 15 mg and 30 mg groups was 38.4% and 40.6%, respectively, and 37.6% in the placebo group. The long-term rate of infection for RINVOQ 15 mg and 30 mg was 73.8 and 82.6 events per 100 patient-years, respectively.

Serious Infections

In the placebo-controlled induction studies, the frequency of serious infection over 8 weeks in the RINVOQ 45 mg group and the placebo group was 1.3% and 1.3%, respectively. No additional serious infections were observed over 8-week extended induction treatment with RINVOQ 45 mg. In the placebo-controlled maintenance study, the frequency of serious infection up to 52 weeks in the RINVOQ 15 mg and 30 mg groups was 3.2%, and 2.4%, respectively, and 3.3% in the placebo group. The long-term rate of serious infection for the RINVOQ 15 mg and 30 mg groups was 4.1 and 3.9 events per 100 patient-years, respectively. The most frequently reported serious infection in the ulcerative colitis studies was COVID-19 pneumonia.

Tuberculosis

In the clinical studies for ulcerative colitis, there was 1 case of active tuberculosis reported in a patient receiving RINVOQ 15 mg during the long-term extension study.

Opportunistic Infections (excluding tuberculosis)

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

In the placebo-controlled induction studies over 8 weeks, the frequency of herpes zoster in the RINVOQ 45 mg group was 0.6% and 0% in the placebo group. The frequency of herpes zoster was 3.9% over 16-week treatment with RINVOQ 45 mg. In the placebo controlled maintenance study up to 52 weeks, the frequency of herpes zoster in the RINVOQ 15 mg and 30 mg groups was 4.4% and 4.0%, respectively, compared to 0% in the placebo group. The long term rate of herpes zoster for the RINVOQ 15 mg and 30 mg groups was 5.7 and 6.3 events per 100 patient-years, respectively.

Malignancy

In the placebo-controlled induction studies with RINVOQ 45 mg over 8 weeks, there were no reports of malignancy. In the placebo-controlled maintenance study up to 52 weeks, the frequency of malignancies excluding NMSC in the RINVOQ 15 mg and 30 mg groups was 0.4% and 0.8%, respectively, and 0.4% in the placebo group. The long-term incidence rate of malignancies excluding NMSC for the RINVOQ 15 mg and 30 mg was 0.3 and 1.0 per 100 patient years, respectively. In a supplemental analysis in patients who received any dose of RINVOQ during any treatment period (N=1299, 2531.7 patient-years, mean exposure 102 weeks), the exposure-adjusted event rate of malignancies excluding NMSC was 0.6 per 100 patient years. In an analysis with limited long-term data of patients who received placebo during any treatment period prior to receiving any dose of RINVOQ (N=375, 131.0 patient-years, mean exposure 18 weeks), no malignancies excluding NMSC were observed prior to their switch to RINVOQ or discontinuation from placebo.

Major adverse cardiovascular events (MACE)
In the placebo-controlled induction studies with RINVOQ 45 mg over 8 weeks, there were no reports of MACE. In the placebo-controlled maintenance study up to 52 weeks, the frequency of MACE in the RINVOQ 30 mg group and the placebo group was 0.4% and 0.4%, respectively. The long-term incidence rate of MACE for the RINVOQ 30 mg was 0.7 per 100 patient years. There were no reports of MACE in the RINVOQ 15 mg group in the performed analyses.
In a supplemental analysis in patients who received any dose of RINVOQ during any treatment period (N=1299, 2531.7 patient-years, mean exposure 102 weeks), the exposure-adjusted event rate of MACE was 0.2 per 100 patient years. In an analysis with limited long-term data of patients who received placebo during any treatment period prior to receiving any dose of RINVOQ (N=375, 131.0 patient-years, mean exposure 18 weeks), no events of MACE were observed prior to their switch to RINVOQ or discontinuation from placebo.

Gastrointestinal Perforations
In the clinical studies for ulcerative colitis, there was 1 case of gastrointestinal perforation reported in a patient receiving RINVOQ 15 mg during the long-term extension study.

Thrombosis
In the placebo-controlled induction studies, the frequency of venous thrombosis (pulmonary embolism or deep vein thrombosis) over 8 weeks in the RINVOQ 45 mg group was 0.1% and 0.3% in the placebo group, respectively. No additional events of venous thrombosis were reported with RINVOQ 45 mg extended induction treatment. In the placebo-controlled maintenance study, the frequency of venous thrombosis up to 52 weeks in the RINVOQ 15 mg and 30 mg groups was 0.8% and 0.8%, respectively, and 0% in the placebo group. The long-term incidence rate of venous thrombosis for RINVOQ 15 mg and 30 mg was 1.0 and 0.7 per 100 patient-years, respectively. In a supplemental

analysis in patients who received any dose of RINVOQ during any treatment period (N=1299, 2531.7 patient-years, mean exposure 102 weeks), the exposure-adjusted event rate of venous thrombosis was 0.6 per 100 patient years. In an analysis with limited long-term data of patients who received placebo during any treatment period prior to receiving any dose of RINVOQ (N=375, 131.0 patient-years, mean exposure 18 weeks), the exposure-adjusted event rate of venous thrombosis was 1.5 per 100 patient-years prior to their switch to RINVOQ or discontinuation from placebo.

Hepatic transaminase elevations

In the placebo-controlled induction studies over 8 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 1.5% and 1.5% of patients treated with RINVOQ 45 mg and 0% and 0.3% with placebo, respectively. In the placebo-controlled maintenance study up to 52 weeks, ALT elevations ≥ 3 x ULN in at least one measurement were observed in 2.0% and 4.0% of patients treated with RINVOQ 15 mg and 30 mg and 0.8% with placebo, respectively. AST elevations ≥ 3 x ULN in at least one measurement were observed in 1.6% and 2.0% of patients treated with RINVOQ 15 mg and 30 mg and 0.4% with placebo, respectively. Most cases of hepatic transaminase elevations were asymptomatic and transient. The pattern and incidence of ALT/AST elevations remained generally stable over time including in long-term extension studies.

Lipid elevations

RINVOQ treatment was associated with increases in lipid parameters including total cholesterol, LDL cholesterol, and HDL cholesterol in placebo-controlled induction and maintenance studies over 8 and up to 52 weeks, respectively. Changes from baseline in lipid parameters are summarized below:

- Mean total cholesterol increased by 0.95 mmol/L in the RINVOQ 45 mg induction group and by 0.87 mmol/L and 1.19 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean HDL increased by 0.44 mmol/L in the RINVOQ 45 mg induction group and by 0.21 mmol/L and 0.34 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean LDL increased by 0.52 mmol/L in the RINVOQ 45 mg induction group and by 0.65 mmol/L and 0.83 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.
- Mean triglycerides decreased by 0.05 mmol/L in the RINVOQ 45 mg induction group and increased by 0.03 mmol/L and 0.08 mmol/L in the RINVOQ 15 mg and 30 mg maintenance groups, respectively.

Creatine phosphokinase elevations

In the placebo-controlled induction studies over 8 weeks, increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 2.2% and 0.3% of patients in the

RINVOQ 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study up to 52 weeks, CPK elevations > 5 x ULN were reported in 4.0% and 6.4% of patients in the RINVOQ 15 mg and 30 mg groups and 1.2% in the placebo group, respectively. Most elevations > 5 x ULN were transient and did not require treatment discontinuation.

Neutropenia

In the placebo-controlled induction studies over 8 weeks, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 2.8% of patients in the RINVOQ 45 mg group and 0% in the placebo group, respectively. In the placebo-controlled maintenance study up to 52 weeks, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.8% and 2.4% of patients in the RINVOQ 15 mg and 30 mg groups and 0.8% in the placebo group, respectively.

Lymphopenia

In the placebo-controlled induction studies over 8 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 2.0% of patients in the RINVOQ 45 mg group and 0.8% in the placebo group. In the placebo-controlled maintenance study up to 52 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 1.6% and 0.8% of patients in the RINVOQ 15 mg and 30 mg groups and to 0.8% in the placebo group, respectively.

Anemia

In the placebo-controlled induction studies over 8 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in 0.3% of patients in the RINVOQ 45 mg group and 2.1% in the placebo group. In the placebo-controlled maintenance study up to 52 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in 0.4% and 0.4% of patients in the RINVOQ 15 mg and 30 mg groups and 1.2% in the placebo group, respectively.

Crohn's disease

Specific Adverse Reactions

Overall, the safety profile observed in patients with CD treated with RINVOQ was consistent with the known safety profile of RINVOQ.

Gastrointestinal Perforations

During the placebo-controlled period in the Phase 3 induction clinical studies, gastrointestinal perforation was reported in 1 patient (0.1%) treated with RINVOQ 45 mg and no patients on placebo

through 12 weeks. In all patients treated with RINVOQ 45 mg (n=938) during the induction studies, gastrointestinal perforation was reported in 4 patients (0.4%).

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

Malignancy

In the placebo-controlled induction studies, there were no reports of malignancy excluding NMSC. In the long-term placebo-controlled period, malignancies excluding NMSC were reported in 1 patient treated with placebo (0.7 per 100 patient-years), 1 patient treated with RINVOQ 15 mg (0.4 per 100 patient-years), and 4 patients treated with RINVOQ 30 mg (1.5 per 100 patient-years).

Non-Melanoma Skin Cancer (NMSC)
In the maintenance therapy trial in patients with Crohn's disease, one case of NMSC was documented in the group of patients (n=51) who, following a lack of response to induction therapy with 45 mg once daily for 12 weeks, received an extended induction of 30 mg once daily for an additional 12 weeks and subsequent maintenance therapy of 30 mg once daily until week 52.

Undesirable effects from the post-marketing phase

The following adverse reactions have been identified during post-approval use of RINVOQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Immune system disorders: Hypersensitivity

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

L04AF03

Mechanism of action

Upadacitinib is a selective and reversible inhibitor of JAK1. 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 and other markers of inflammation

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.

In patients with Crohn's disease, reductions in hsCRP and faecal calprotectin (FCP) were observed after induction treatment with upadacitinib. Decreases in hsCRP and FCP were maintained out to Week 52 in the maintenance study.

Cardiac electrophysiology

The effect of upadacitinib on QTc interval was evaluated in subjects who received single and multiple doses of upadacitinib. At 2.5 times the mean exposure of the maximum therapeutic dose, 45 mg once daily dose, there was no clinically relevant effect on the QTc interval.

Vaccine Studies

The influence of RINVOQ on the humoral response following administration of adjuvanted recombinant glycoprotein E herpes zoster vaccine was evaluated in 93 patients over 50 years of age with rheumatoid arthritis under stable treatment (median treatment duration: 3.9 years) with RINVOQ 15 mg. 98% of patients (n=91) were on concomitant methotrexate. 49% of patients were on oral corticosteroids at baseline. Regardless of the concomitant medication, the vaccination resulted in 88% (95% CI: 81.0, 94.5) of patients treated with RINVOQ 15 mg having an at least 4-fold increase in pre-vaccination concentration of anti-glycoprotein E titer levels at Week 16 (4 weeks post-dose 2 vaccination). The extent to which this vaccine response allows protection against infection or reactivation is unclear.

The influence of RINVOQ on the humoral response following the administration of inactivated pneumococcal 13-valent conjugate vaccine was evaluated in 111 patients with rheumatoid arthritis under stable treatment with RINVOQ 15 mg (n=87) or 30 mg (n=24). 97% of patients (n=108) were on concomitant methotrexate. Vaccination resulted in 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with RINVOQ 15 mg and 30 mg, respectively having an at least 2-fold increase in antibody concentration compared to the pre-vaccination baseline for at least 6 of the individual pneumococcal antigens of the vaccine. The extent to which this vaccine response allows protection against infection is unclear.

Clinical efficacy

Rheumatoid Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in five Phase 3 randomized, double-blind, multicenter studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria (see Table 5). Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. Four studies included long term extensions for up to 5 years, and one study (SELECT-COMPARE) included a long-term extension for up to 10 years.

Table 5. 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] (661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	Primary Endpoint: • 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 6). 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. At 3 years, 297/651 (45.6%) and 111/327 (33.9%) patients remained on originally randomized treatment of RINVOQ 15 mg or adalimumab, respectively, in SELECT-COMPARE, and 216/317 (68.1%) and 149/315 (47.3%) patients remained on originally randomised treatment of RINVOQ 15 mg or MTX monotherapy, respectively, in SELECT-EARLY. Among the patients who remained on their originally allocated treatment, low disease activity and clinical remission were maintained through 3 years.

ACR Response

In all studies, more patients treated with RINVOQ 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo, MTX or adalimumab (Table 7). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained through 3 years among the patients who remained on their originally allocated treatment.

Treatment with 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 7).

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 6. 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; bDMARD = biologic disease-modifying anti-rheumatic drug; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = c-reactive protein, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug;DAS28 = Disease Activity Score 28 joints; IR= inadequate responder; 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 7: 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]/	-28	-40[h]					-19	-37[h,l]	-32		

26[e]											
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; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-reactive protein; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; 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 8). 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). Inhibition of progression of structural joint damage was maintained through Week 96 in both studies for patients who remained on their originally allocated treatment with RINVOQ 15 mg (based on available results from 327 patients in SELECT-COMPARE and 238 patients in SELECT-EARLY).

Table 8: 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.

Improvements in HAQ-DI and pain were maintained through 3 years for patients who remained on their originally allocated treatment with RINVOQ 15 mg based on available results from SELECT-COMPARE and SELECT-EARLY.

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 9). 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 9: 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 10, 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 11). 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

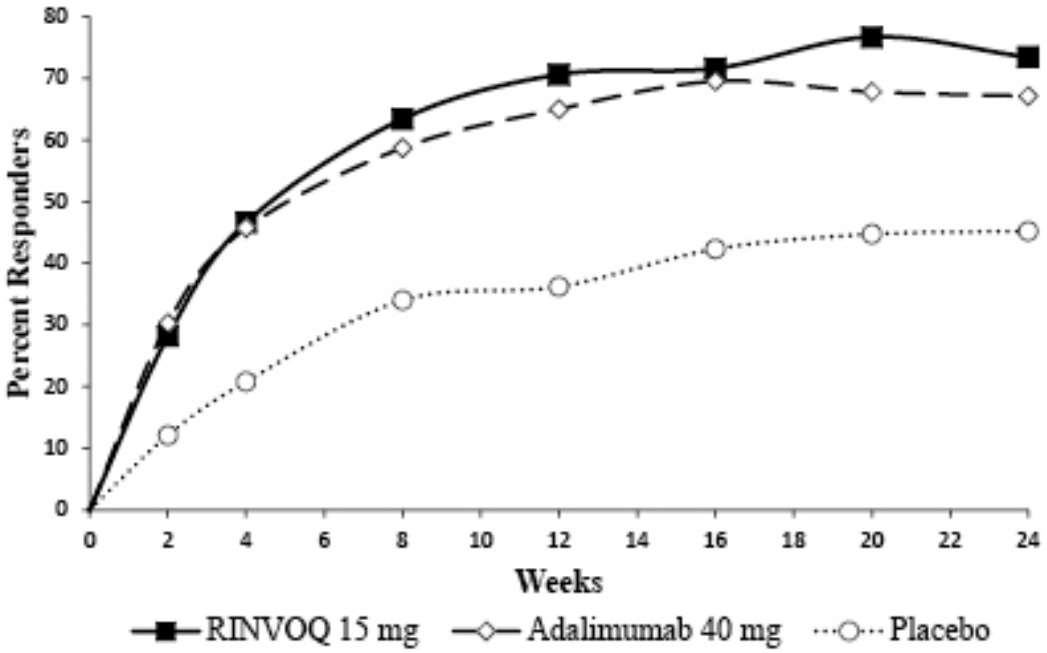


Table 10: Clinical response

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 11: 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 12). 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 12: 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 11), 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 two randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with active ankylosing spondylitis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and Patient's Assessment of Total Back Pain score ≥4 (Table 13). Both studies included an open-label extension for up to 2 years after a double-blind, placebo-controlled 14-week period.

Table 13: 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 (function) • SPARCC MRI score (spine) • AS Quality of Life • BASMI (spinal mobility) • MASES (enthesitis) • WPAI • ASAS Health Index
SELECT-AXIS 2	bDMARD-IR[a,c] (420)	• Upadacitinib 15 mg • Placebo	Primary Endpoint: ASAS40 at Week 14
			Key Secondary Endpoints at Week 14: • ASAS Partial Remission • BASDAI 50 • ASDAS-CRP • BASFI (function) • SPARCC MRI score (spine) • AS Quality of Life • BASMI (spinal mobility) • MASES (enthesitis)

			• ASAS Health Index • ASAS20 • ASDAS Inactive Disease • Total Back Pain • Nocturnal Back Pain • ASDAS Low Disease Activity

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.

[c] At baseline, 77.4% had lack of efficacy to either a TNF blocker or interleukin-17 inhibitor (IL-17i); 30.2% had intolerance; 12.9% had prior exposure but not lack of efficacy to two bDMARDs.

Clinical Response

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved an ASAS40 response compared to placebo at Week 14 (51.6% vs 25.5%; p<0.001 for SELECT-AXIS 1 and 44.5% vs 18.2%; p<0.001 for SELECT-AXIS 2) (Table 14, Figures 2 and 3). Greater responses were seen as early as Week 2 in SELECT-AXIS 1 (16.1% vs 1.1 %; nominal p-value <0.001) and Week 4 in SELECT-AXIS 2 (21.8% vs 12.4 %; nominal p-value = 0.01) for ASAS40.

In both studies, 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.

In both studies, the efficacy of RINVOQ 15 mg was demonstrated regardless of subgroups evaluated including gender, baseline BMI, symptom duration of ankylosing spondylitis, baseline hsCRP, and in SELECT-AXIS 2 also prior use of bDMARDs.

Figure 2: Percent of Patients Achieving ASAS40 in SELECT-AXIS 1

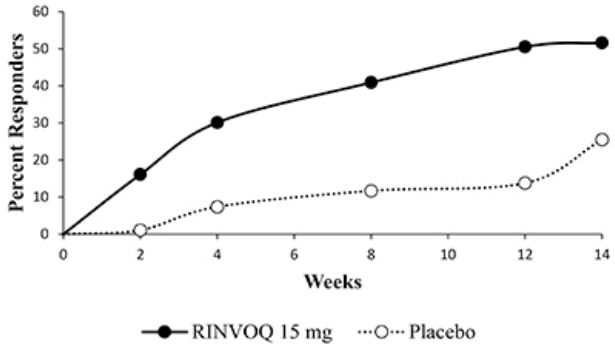


Figure 3: Percent of Patients Achieving ASAS40 in SELECT-AXIS 2

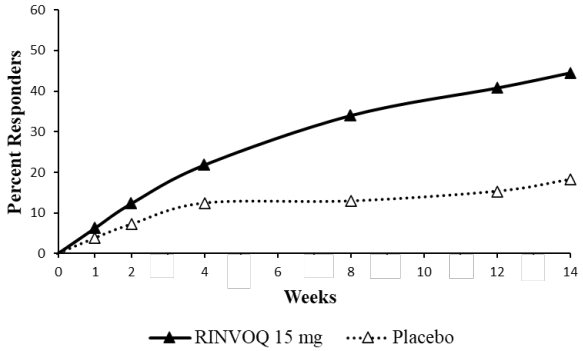


Table 14: Clinical Response

Study	**SELECT-AXIS 1 bDMARD-naïve**		**SELECT-AXIS 2 bDMARD-IR**	
Treatment Group	**PBO**	**UPA 15 mg**	**PBO**	**UPA 15 mg**
N	94	93	209	211
ASAS40 (% of patients)				
Week 14	25.5	51.6[a]	18.2	44.5[a]
ASAS20 (% of patients)				
Week 14	40.4	64.5[c]	38.3	65.4[a]
ASAS Partial Remission (% of patients)				
Week 14	1.1	19.4[a]	4.3	17.5[a]
BASDAI 50 (% of patients)				
Week 14	23.4	45.2[b]	16.7	43.1[a]
ASDAS-CRP (Change from Baseline)				
Week 14	-0.54	-1.45[a]	-0.49	-1.52[a]
ASDAS Inactive Disease (% of patients)				
Week 14	-	-	1.9	12.8[a]
ASDAS Low Disease Activity (% of patients)				
Week 14	-	-	10.1	44.1[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; IR= inadequate responder; PBO = placebo; UPA= upadacitinib

[a] p≤0.001 upadacitinib vs placebo comparison
[b] p≤0.01 upadacitinib vs placebo comparison
[c] Upadacitinib vs placebo comparison was not controlled for multiplicity.
For binary endpoints, Week 14 results are based on non-responder imputation (SELECT-AXIS 1) and on non-responder imputation in conjunction with multiple imputation (SELECT-AXIS 2). For continuous endpoints, Week 14 results are based on the least squares mean change from baseline using mixed models for repeated measure analysis.

In SELECT-AXIS 1, response rates for ASAS40, ASAS20, ASAS partial remission, BASDAI 50, ASDAS Inactive Disease, ASDAS Low Disease Activity, change from baseline in ASDAS-CRP, and hsCRP in patients treated with RINVOQ 15 mg were maintained through Week 104.

Physical Function and Health-Related Outcomes
In both studies, significant improvement (p = 0.001 for SELECT-AXIS 1 and p <0.0001 for SELECT-AXIS 2) 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 in SELECT-AXIS 1 and -2.26 in SELECT-AXIS 2) compared to placebo (-1.30 and -1.09). Standard deviation of within group change from baseline at Week 14 were 2.44 and 2.28 in patients treated with RINVOQ 15 mg, and 2.05 and 1.67 in patients treated with placebo, in SELECT-AXIS 1 and SELECT-AXIS 2, respectively.

In SELECT-AXIS 1, 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.

In SELECT-AXIS 2, patients treated with RINVOQ 15 mg showed significant improvements in total back pain and nocturnal back pain compared to placebo at Week 14. Responses were observed as early as Week 1 for total back pain and Week 2 for nocturnal back pain.

In both studies, 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.
In SELECT-AXIS 1, responses observed at Week 14 in BASFI, total back pain, and nocturnal back pain were maintained through Week 104 for patients receiving RINVOQ 15 mg.

In SELECT-AXIS 2, patients treated with RINVOQ 15 mg showed significant improvements from baseline in health-related quality of life and overall health as measured by ASQoL and ASAS Health Index, respectively, compared to placebo at Week 14.

Enthesitis

In SELECT-AXIS 2, patients with pre-existing enthesitis treated with RINVOQ 15 mg showed significant improvement in enthesitis compared to placebo as measured by change from baseline in MASES at week 14.

Spinal mobility

In SELECT-AXIS 2, patients treated with RINVOQ 15 mg showed significant improvement in spinal mobility compared to placebo as measured by change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14.

In SELECT-AXIS 1, improvements from baseline were observed in pre-defined secondary endpoints of BASMI, MASES, ASQoL, ASAS HI, and WPAI for patients receiving RINVOQ 15 mg compared to placebo at Week 14, but these were not statistically significant in the multiplicity adjusted analyses and responses observed at Week 14 were maintained through Week 104 for patients receiving RINVOQ 15 mg.

Objective Measure of Inflammation

Signs of inflammation were assessed by MRI and expressed as change from baseline in the SPARCC score for spine. In both studies, at Week 14, significant improvement of inflammatory signs in the spine was observed in patients treated with RINVOQ 15 mg compared to placebo. In SELECT-AXIS 1, responses in inflammation as assessed by MRI observed at Week 14 were maintained through Week 104.

Atopic Dermatitis

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

In all three studies, patients received RINVOQ once daily doses of 15 mg, 30 mg or matching placebo for 16 weeks. In the AD UP study, patients also received concomitant topical corticosteroids (TCS). Following completion of the double-blinded period, patients originally randomized to RINVOQ were to continue receiving the same dose until week 136. Patients in the placebo group were re-randomized in a 1:1 ratio to receive RINVOQ 15 mg or 30 mg until week 136.

Table 15. Clinical Trial Summary

Study Name	**Treatment Arms**	**Key Outcome Measures**
MEASURE UP 1 and MEASURE UP 2	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Co-Primary Endpoints at Week 16: • EASI 75 • vIGA-AD 0/1
		Key Secondary Endpoints (at Week 16 except where noted) • EASI 90/100 • EASI 75 at Week 2 • % change in EASI • % change in SCORAD • Worst Pruritus NRS improvement ≥ 4 at Week 1 and 16 • Worst Pruritus NRS improvement ≥ 4 at Day 2 (30 mg), Day 3 (15 mg) • % change in Worst Pruritus NRS • EASI increase ≥ 6.6 points (flare) during double-blind period • ADerm-SS TSS-7 improvement ≥ 28 • ADerm-SS Skin Pain improvement ≥ 4 • ADerm-IS Sleep improvement ≥ 12 • ADerm-IS Emotional State improvement ≥ 11 • ADerm-IS Daily Activities improvement ≥ 14 • POEM improvement ≥ 4 • HADS-A < 8 and HADS-D < 8 • DLQI 0/1 • DLQI improvement ≥ 4
AD UP	• Upadacitinib 15 mg + TCS	Co-Primary Endpoints at Week 16: • EASI 75 • vIGA-AD 0/1

	• Upadacitinib 30 mg + TCS • Placebo + TCS	Key Secondary Endpoints (at Week 16 except where noted) • EASI 75 at Week 2 and 4 • EASI 90 at Week 4 and 16 • EASI 100 (30 mg) • % change in EASI • Worst Pruritus NRS improvement ≥ 4 at Week 1, 4 and 16 • % change in Worst Pruritus NRS
Abbreviations: SCORAD = SCORing Atopic Dermatitis, POEM: Patient Oriented Eczema Measure, DLQI: Dermatology Life Quality Index, HADS: Hospital Anxiety and Depression Scale, ADerm-SS = Atopic Dermatitis Symptom Scale, ADerm-IS: Atopic Dermatitis Impact Scale		

Baseline characteristics

In the monotherapy studies (MEASURE UP 1 and 2), 50.0% of patients had a baseline a vIGA-AD score of 3 (moderate) and 50.0% of patients had a vIGA-AD of 4 (severe). The mean baseline EASI score was 29.3 and the mean baseline weekly average Worst Pruritus NRS was 7.3. In the monotherapy studies, across all treatment groups, the mean age was 33.8, the mean weight was 74.8 kg, 44.9% were female, 67.3% were white, 22.9% were Asian, and 6.3% were black.

In the concomitant TCS study (AD UP), 47.1% of patients had a baseline vIGA-AD score of 3 (moderate) and 52.9% of patients had a vIGA-AD of 4 (severe). The mean baseline EASI score was 29.7 and the mean baseline weekly average Worst Pruritus NRS was 7.2%. In the AD UP study, across all treatment groups, the mean age was 34.1, the mean weight was 75.5 kg, 39.3% were female, 71.8% were white, 20.5% were Asian, and 5.5% were black.

Clinical Response

Monotherapy Studies (MEASURE UP 1 AND MEASURE UP 2)

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

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

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

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

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

Study	**MEASURE UP 1**		**MEASURE UP 2**	
Treatment Group	PBO	UPA 15 mg	PBO	UPA 15 mg
Number of subjects randomized	281	281	278	276
% responders				
vIGA-AD 0/1[a,b]	8.4	48.1[f]	4.7%	38.8[f]
EASI 75[a]	16.3	69.6[f]	13.3%	60.1[f]
EASI 90[a]	8.1	53.1[f]	5.4	42.4[f]
EASI 100[a]	1.8	16.7[f]	0.7	14.1[f]
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	11.8 N=272	52.2[f] N=274	9.1 N=274	41.9[f] N=270
Worst Pruritus NRS 0 or 1[d]	5.5 N=275	36.6[g] N=279	4.3 N=277	26.9[g] N=275
Mean percent change (SE)[e]				
EASI	-40.7 (2.28)	-80.2[f] (1.91)	-34.5 (2.59)	-74.1[f] (2.20)
SCORAD	-32.7 (2.33)	-65.7[f] (1.78)	-28.4 (2.50)	-57.9[f] (2.01)
Worst Pruritus NRS	-26.1 (5.41)	-62.8[f] (4.49)	-17.0 (2.73)	-51.2[f] (2.34)

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

[a] Based on number of subjects randomized

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

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

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

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

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

[g] nominal p<0.001 upadacitinib vs placebo comparison

Figure 4: Proportion of patients achieving an EASI 75 response in monotherapy studies

MEASURE UP 1 **MEASURE UP 2**

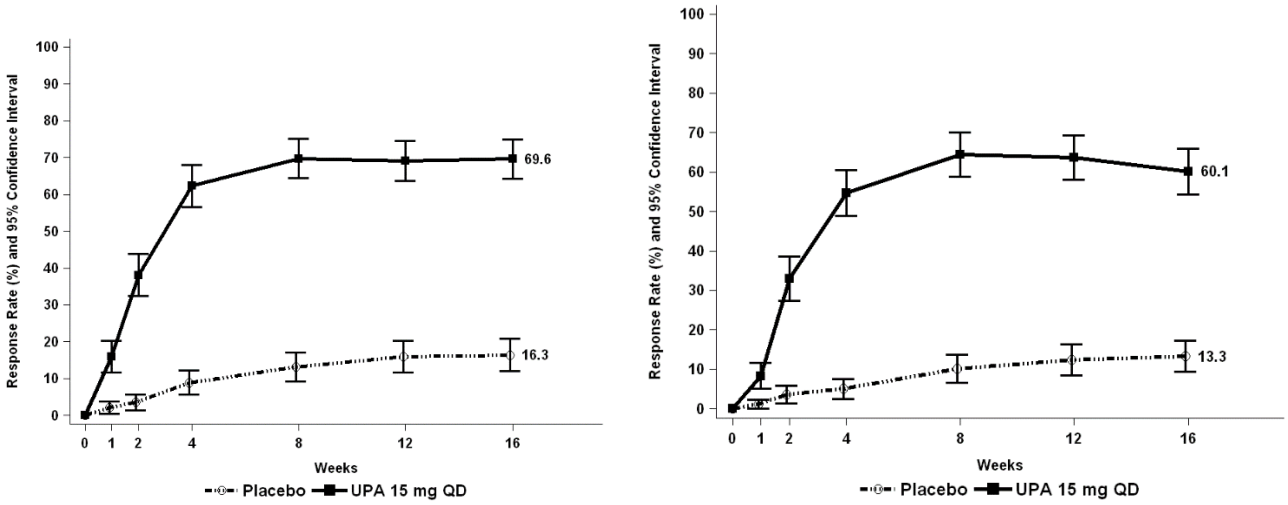
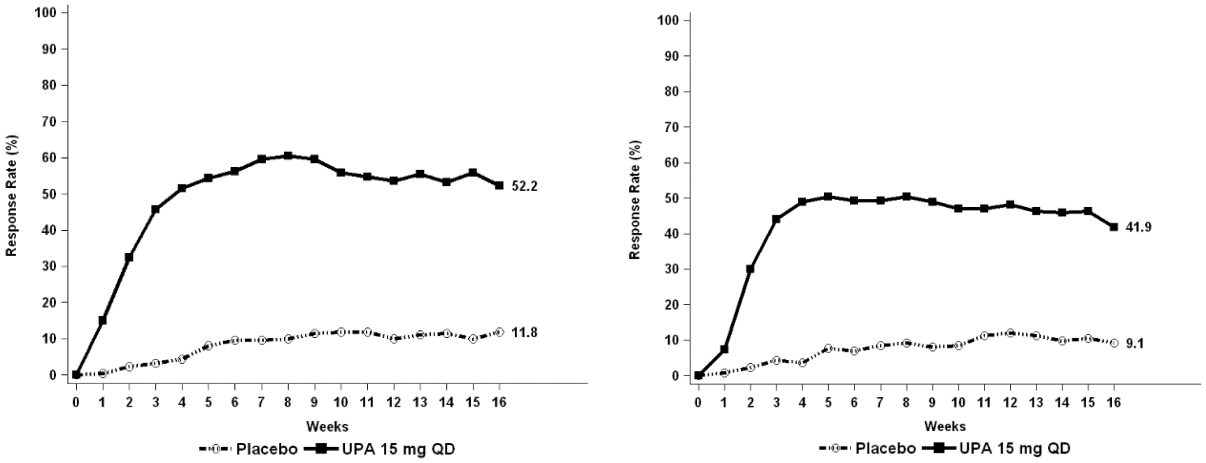


Figure 5: Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in monotherapy studies

MEASURE UP 1 **MEASURE UP 2**



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

Concomitant TCS Study (AD UP)

In AD UP, a significantly greater proportion of patients treated with RINVOQ 15 mg + TCS achieved vIGA-AD 0 or 1 response and achieved EASI 75 compared to placebo + TCS at week 16 (Table 17). A rapid improvement in skin clearance (defined as EASI 75 by week 2) was achieved compared to placebo + TCS ($p < 0.001$). In addition, a higher EASI 90 response rate was achieved at week 4 compared to placebo + TCS ($p < 0.001$).

A significantly greater proportion of patients treated with RINVOQ 15 mg + TCS achieved a clinically meaningful improvement in itch (defined as a ≥ 4-point reduction in the Worst Pruritus NRS) compared to placebo + TCS at week 16. A rapid improvement in itch (defined as a ≥ 4-point reduction in Worst Pruritus NRS by week 1) was achieved compared to placebo + TCS ($p < 0.001$).
Figure 6 and Figure 7 show proportion of patients achieving an EASI 75 response and the proportion of patients with ≥4-point improvement in the Worst Pruritus NRS, respectively up to week 16.

Table 17: Efficacy results of RINVOQ + concomitant TCS at week 16

Treatment Group	**Placebo + TCS**	**UPA 15 mg + TCS**
Number of subjects randomized	304	300
% responders		
vIGA-AD 0/1[a,b]	10.9	39.6[f]
EASI 75[a]	26.4	64.6[f]
EASI 90[a]	13.2	42.8[f]
EASI 100[a]	1.3	12.0[g]
Worst Pruritus NRS[c] *(≥ 4-point improvement)*	15.0 N=294	51.7[f] N=288
Worst Pruritus NRS 0 or 1[d]	7.3 N=300	33.1[g] N=296
Mean percent change (SE)[e]		
EASI	-45.9 (2.16)	-78.0[f] (1.98)
SCORAD	-33.6 (1.90)	-61.2[g] (1.70)
Worst Pruritus NRS	-25.1 (3.35)	-58.1[f] (3.11)

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

[a] Based on number of subjects randomized

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

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

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

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

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

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

Figure 6: Proportion of patients achieving an EASI 75 response AD UP Study

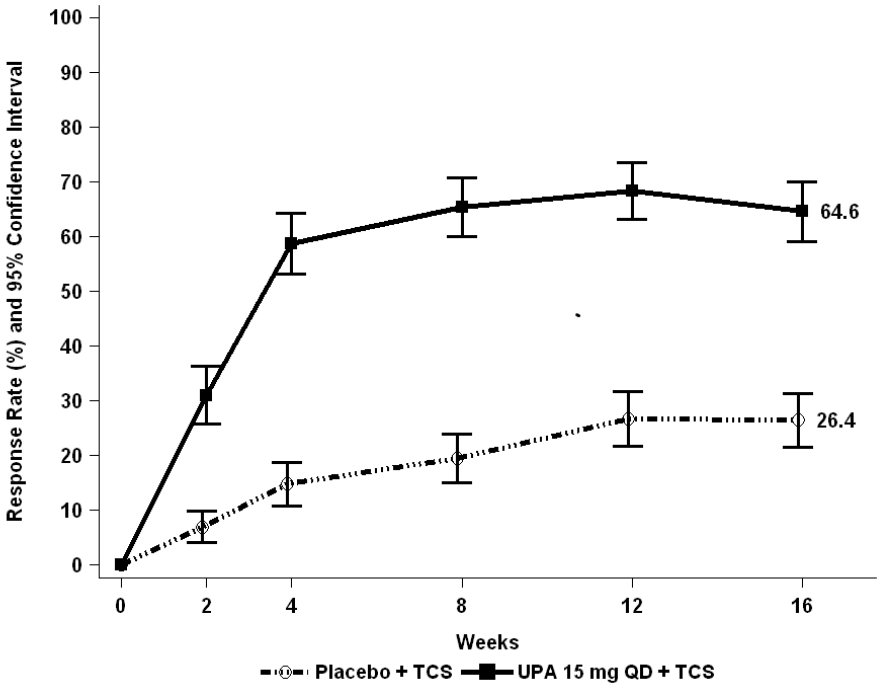
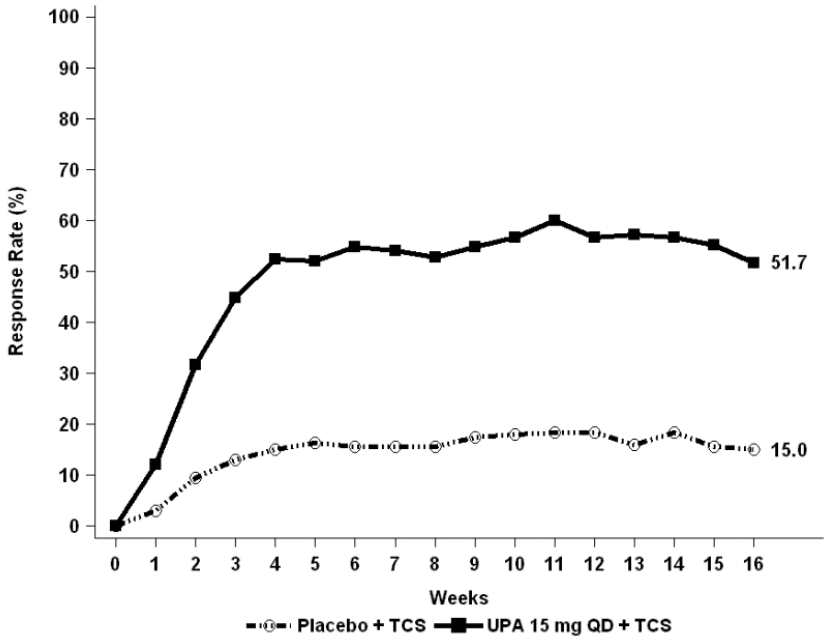


Figure 7: Proportion of patients with ≥4-point improvement in the Worst Pruritus NRS in AD UP Study



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

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

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

Quality of Life/Patient reported outcomes

In the MEASURE UP studies, a significantly greater proportion of patients treated with RINVOQ 15 mg reported clinically meaningful reductions in the symptoms of AD and the impact of AD on health-related quality of life compared to placebo at week 16 (Table 18). A significantly greater proportion of patients treated with RINVOQ achieved clinically meaningful reductions in AD symptom severity as measured by ADerm-SS TSS-7 and ADerm-SS Skin Pain compared to placebo at week 16. A greater proportion of patients treated with RINVOQ achieved clinically meaningful reductions in the patient-reported effects of AD on sleep, daily activities and emotional state as measured by the ADerm-IS domain scores compared to placebo at week 16. Similarly, compared to placebo at week 16, a greater proportion of patients treated with RINVOQ achieved clinically meaningful improvements in AD symptom frequency and health-related quality of life as measured by the POEM and DLQI. Anxiety and depression symptoms as measured by the HADS score were significantly reduced; in patients with baseline HADS-anxiety or HADS-depression subscale scores ≥ 8 (the cut-off value for

anxiety or depression), a greater proportion of patients in the RINVOQ 15 mg group achieved HADS-anxiety and HADS-depression scores < 8 at week 16 compared to placebo (Table 18).

Table 18: Patient-reported outcomes results of RINVOQ monotherapy studies at week 16

Study	**MEASURE UP 1**		**MEASURE UP 2**	
Treatment group	PBO	UPA 15 mg	PBO	UPA 15 mg
Number of subjects randomized	281	281	278	276
% responders				
ADerm-SS TSS-7 *(≥ 28-point improvement)* [a,b]	15.0 N=226	53.6[h] N=233	12.7% N=244	53.0[h] N=230
ADerm-SS Skin Pain *(≥ 4-point improvement)*[a]	15.0 N=233	53.6 [h] N=237	13.4% N=247	49.4[h] N=237
ADerm-IS Sleep *(≥ 12-point improvement)* [a,c]	13.2 N=220	55.0[h] N=218	12.4% N=233	50.2[h] N=219
ADerm-IS Daily Activities *(≥ 14-point improvement)*[a,d]	20.3 N=197	65.0[h] N=203	18.9% N=227	57.0[h] N=207
ADerm-IS Emotional State *(≥ 11-point improvement)* [a,e]	19.8 N=212	62.6[h] N=227	16.7% N=234	57.0[h] N=228
DLQI *(DLQI 0/1)*[f]	4.4 N=252	30.3[h] N=258	4.7% N=257	23.8[h] N=252
DLQI *(≥ 4-point improvement)* [a]	29.0 N=250	75.4[h] N=254	28.4% N=250	71.7[h] N=251
POEM *(≥ 4-point improvement)* [a]	22.8% N=276	75.0[h] N=278	28.7% N=268	70.9[h] N=268
HADS *(HADS-A < 8 and HADS-D < 8)* [g]	14.3 N=126	45.5[h] N=145	11.4% N=140	46.0[h] N=137
Abbreviations: UPA= upadacitinib (RINVOQ); PBO = placebo The threshold values specified correspond to the minimal clinically important difference (MCID) and was used to determine response.				

[a] N = number of patients whose baseline score is greater than or equal to the MCID.
[b] ADerm-SS TSS-7 assesses itch while asleep, itch while awake, skin pain, skin cracking, pain caused by skin cracking, dry skin, and flaking due to AD.
[c] ADerm-IS Sleep assesses difficulty falling asleep, sleep impact, and waking up at night due to AD.
[d] ADerm-IS Daily Activities assesses AD's effect on household activities, physical activities, social activities, and concentration.
[e] ADerm-IS Emotional State assesses self-consciousness, embarrassment, and sadness due to AD.
[f] N = number of patients whose baseline DLQI score is > 1.
[g] N = number of patients whose baseline HADS-A or HADS-D is ≥ 8.
[h] multiplicity-controlled p < 0.001 upadacitinib vs placebo comparison.

Ulcerative Colitis

The efficacy and safety of RINVOQ was evaluated in three multicenter, double-blind, placebo-controlled Phase 3 clinical studies: two replicate induction studies, UC-1 (U-ACHIEVE Induction) and UC-2 (U-ACCOMPLISH), and a maintenance study UC-3 (U-ACHIEVE Maintenance).
Disease activity was based on the adapted Mayo score (aMS, Mayo scoring system excluding Physician's Global Assessment), which ranged from 0 to 9 and has three subscores that were each scored 0 (normal) to 3 (most severe): stool frequency subscore (SFS), rectal bleeding subscore (RBS), and a centrally-reviewed endoscopy subscore (ES).

Table 19: Clinical Trial Summary

Study Name	**Population (n)**	**Treatment Arms**	**Key Outcome Measures**
Induction			
U-ACHIEVE (UC-1)	Biologic failure* (246/473) Without biologic failure+(227/473)	• Upadacitinib 45 mg • Placebo	Primary Endpoint: • Clinical remission per Adapted Mayo score at Week 8

U-ACCOMPLISH (UC-2)	Biologic failure (262/515) Without biologic failure(253/515)		Secondary Endpoints at Week 8 or specified: • Endoscopic Improvement • Endoscopic remission • Clinical response • Clinical response at Week 2 • Histologic-endoscopic mucosal improvement • No bowel urgency • No abdominal pain • Histologic improvement • Change from baseline in IBDQ total score • Mucosal healing • Change from baseline in FACIT-F score
Maintenance			
U-ACHIEVE (UC-3)	Biologic failure (225/451) Without biologic failure (226/451)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo	Primary Endpoint: • Clinical remission per Adapted Mayo score at Week 52
			Secondary Endpoints at Week 52: • Endoscopic improvement • Maintenance of clinical remission • Corticosteroid-free clinical remission • Maintenance of endoscopic improvement • Endoscopic remission • Maintenance of clinical response

			• Histological-endoscopic mucosal improvement • Change from baseline in IBDQ total • Mucosal healing • No bowel urgency • No abdominal pain • Change from baseline in FACIT-F

*Biologic failure: inadequate response to, loss of response to, or intolerance to prior biologic therapy
[+]Without biologic failure: inadequate response, loss of response, or intolerance to conventional therapy but had not failed biologic therapy
Abbreviations: IBDQ: inflammatory bowel disease questionnaire, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue score

Induction studies (UC-1 and UC-2)

In studies UC-1 and UC-2, 979 adult and 9 adolescent patients (473 and 515 patients, respectively) were randomized to RINVOQ 45 mg once daily or placebo for 8 weeks with a 2:1 treatment allocation ratio and included in the efficacy analysis. All eligible patients had moderately to severely active ulcerative colitis defined as aMS of 5 to 9 with an ES of 2 or 3 and demonstrated prior treatment failure including inadequate response, loss of response, or intolerance to prior conventional and/or biologic treatment. Patients with previous JAK inhibitor therapy were excluded from the studies.

Among the 979 adult patients, 500 had an inadequate response or were intolerant to treatment with one or more biologics (prior biologic failure) (246 and 254 patients, respectively). At Baseline, 46% and 47% of patients received corticosteroids, 1% and 1% of patients received methotrexate and 57% and 61% of patients received aminosalicylates. Concomitant use of thiopurine was not allowed during the studies. Patient disease activity was moderate (aMS ≤7) in 59% and 59% of patients and severe (aMS >7) in 41% and 41% of patients.

Results of the primary endpoint of clinical remission and secondary endpoints at Week 8 in adult patients with prior biologic failure are listed in Table 20. The pooled results of clinical response over time per paMS in UC-1 and UC-2 are shown in Figure 8.

Table 20. Proportion of Adult Patients with Prior Biologic Failure Meeting Primary and Secondary Efficacy Endpoints at Week 8 in Induction Studies UC-1 and UC-2.

	UC-1 (U-ACHIEVE)			UC-2 (U-ACCOMPLISH)		
Endpoint	**PBO N=78**	**UPA 45 mg N=168**	**Treatment Difference (95% CI)**	**PBO N=86**	**UPA 45 mg N=168**	**Treatment Difference (95% CI)**
Disease Activity and UC Symptoms						
Clinical remission[a]	0.4%	17.9%	17.5%* (11.4, 23.6)	2.5%	29.9%	27.3%* (19.6, 35.1)
Clinical response[b]	12.8%	64.4%	51.6%* (41.2, 61.9)	19.9%	69.0%	49.1%* (38.1, 60.1)
No bowel urgency	14.1%	40.2%	26.1%* (15.4, 36.8)	17.4%	50.0%	32.6%* (21.5, 43.6)
No abdominal Pain	20.5%	42.6%	22.1%* (10.4, 33.8)	18.6%	53.0%	34.4%* (23.2, 45.5)
Endoscopic and Histologic Assessment						
Endoscopic remission[c]	0	8.9%	8.9%** (4.6, 13.3)	1.2%	12.5%	11.3%** (5.8, 16.8)
Endoscopic improvement[d]	1.7%	27.0%	25.3%* (17.8, 32.7)	5.0%	37.0%	32.0%* (23.3, 40.7)
Histologic improvement[e]	17.5%	51.0%	33.5%* (22.1, 44.9)	21.0%	58.9%	37.9%* (26.4, 49.4)
Histologic-endoscopic mucosal improvement[f]	1.4%	22.7%	21.3%* (14.4, 28.2)	4.8%	30.4%	25.6%* (17.3, 34.0)
Mucosal healing[g]	0	6.5%	6.5%*** (2.8, 10.3)	1.2%	8.9%	7.8%*** (2.9, 12.6)
Quality of Life						
Change from Baseline in FACIT-F score	N = 65 1.3	N = 154 9.6	8.3* (5.66, 11.01)	N = 76 3.3	N = 154 9.8	6.6* (4.15, 8.99)
Change from Baseline in IBDQ total score	N = 65 14.6	N = 155 55.7	41.1* (31.53, 50.64)	N = 76 17.4	N = 156 53.5	36.1* (27.57, 44.72)

Abbreviation: PBO = placebo

*p ≤ 0.001, treatment difference (95% CI)

**p ≤ 0.01

***p ≤ 0.05

[a] Per aMS: SFS ≤ 1 and not greater than Baseline, RBS = 0, ES of ≤ 1 without friability

[b] Per aMS: decrease ≥ 2 points and ≥ 30% from Baseline and a decrease in RBS ≥ 1 from Baseline or an absolute RBS ≤ 1

[c] ES of 0

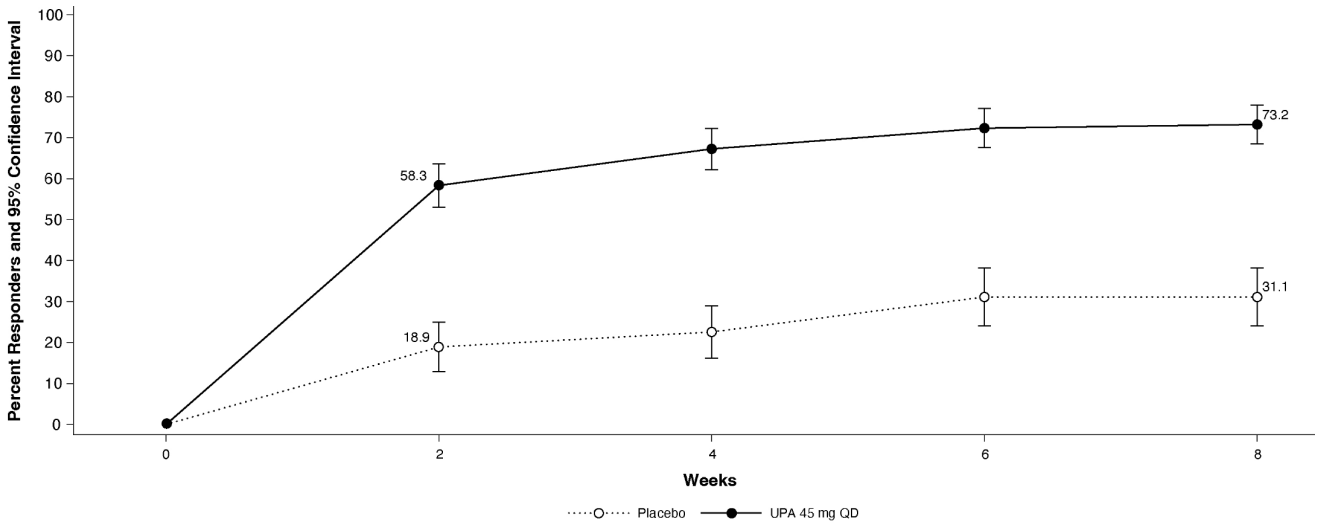
[d] ES ≤1 without friability

[e] Decrease from baseline in Geboes score. Histology was assessed using the Geboes score.

[f] ES ≤1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue).

[g] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue).

Figure 8: Proportion of Adult Patients with Prior Biologic Failure who Achieved Clinical Response per paMS (SFS and RBS) Over Time in Induction Studies UC-1 and UC-2



Extended Induction

A total of 124 adult patients in UC-1 and UC-2 who did not achieve clinical response after 8 weeks of treatment with RINVOQ 45 mg once daily entered an 8-week open-label extended induction period. In patients with prior biologic failure who received the treatment of an additional 8 weeks (16 weeks total) of RINVOQ 45 mg once daily (82 patients), 48.7% of patients achieved clinical response per aMS. Among patients who responded to treatment of 16-week RINVOQ 45 mg once daily, 36.4% of patients (N=11) and 86.7% of patients (N=15) maintained clinical response per aMS with maintenance treatment of RINVOQ 15 mg and 30 mg once daily, respectively. Following the treatment of 16-week RINVOQ 45 mg once daily, 20.0% of patients (N=15) and 41.2% of patients

(N=17) achieved clinical remission per aMS at Week 52 with maintenance treatment of RINVOQ 15 mg and 30 mg once daily, respectively.

Maintenance Study (UC-3)

The efficacy analysis for UC-3 evaluated 223 adult patients with prior biologic failure who achieved clinical response per aMS with 8-week RINVOQ 45 mg once daily induction treatment. Patients were randomized to receive RINVOQ 15 mg, 30 mg or placebo once daily for up to 52 weeks.
The primary endpoint was clinical remission at Week 52. Primary and secondary endpoints are listed in Table 21. Symptomatic remission per paMS over time is shown in Figure 9.

Table 21. Proportion of Adult Patients with Prior Biologic Failure Meeting Primary and Secondary Efficacy Endpoints at Week 52 in Maintenance Study UC-3

Endpoint	PBO N=80	UPA 15 mg N=71	UPA 30 mg N=72	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Disease Activity and UC Symptoms					
Clinical remission[a]	7.6%	40.5%	49.8%	32.9%* (20.0, 45.8)	42.2%* (29.1, 55.4)
Maintenance of clinical remission[b]	N = 21 14.3%	N = 17 76.5%	N = 20 73.0%	62.2%* (37.1, 87.3)	58.7%* (33.6, 83.9)
Corticosteroid-free clinical remission[c]	N = 21 14.3%	N = 17 70.6%	N = 20 73.0%	56.3%* (30.0, 82.6)	58.7%* (33.6, 83.9)
Maintenance of clinical response[d]	N = 70 14.4%	N = 64 60.9%	N = 65 69.9%	46.6%* (32.0, 61.1)	55.5%* (41.5, 69.6)
No bowel urgency	47.5%	59.2%	56.9%	11.7% (-4.2, 27.5)	9.4% (-6.4, 25.3)
No abdominal pain	46.3%	53.5%	50.0%	7.3% (-8.7, 23.2)	3.7% (-12.1, 19.6)
Endoscopic and Histologic Assessment					

Maintenance of endoscopic improvement[e]	N = 31 9.7%	N = 24 70.8%	N = 29 60.7%	61.2%* (40.2, 82.1)	51.0%* (30.1, 72.0)
Endoscopic remission[f]	2.5%	21.5%	20.3%	19.0%* (8.7, 29.3)	17.8%* (7.5, 28.0)
Histologic-endoscopic mucosal improvement[g]	5.3%	32.9%	48.2%	27.6%* (15.5, 39.8)	43.0%* (30.1, 55.8)
Endoscopic improvement[h]	7.9%	43.3%	56.9%	35.4%* (22.3, 48.5)	48.9* (35.6, 62.2)
Mucosal healing[i]	2.5%	17.2%	16.3%	14.7%** (5.2, 24.2)	13.8%** (4.3, 23.3)
Quality of Life					
Change from Baseline in FACIT-F score	3.2	8.2	9.8	5.0** (1.51, 8.53)	6.6* (3.06, 10.10)
Change from Baseline in IBDQ total score	17.0	47.0	56.0	30.0* (16.09, 43.90)	39.0* (24.62, 53.30)

* $p \leq 0.001$, treatment difference (95% CI)

** $p \leq 0.01$

[a] Per aMS: SFS≤ 1 and not greater than Baseline, RBS = 0, ES of ≤ 1 without friability

[b] Clinical remission per aMS at Week 52 among patients who achieved clinical remission at the end of the induction treatment

[c] Clinical remission per aMS at Week 52 and corticosteroid-free for ≥90 days immediately preceding Week 52 among patients who achieved clinical remission at the end of the induction treatment.

[d] Clinical response per aMS at Week 52 among patients who achieved clinical response at the end of the induction treatment

[e] Maintain mucosal healing, ES ≤ 1 without friability, among patients with mucosal healing in induction

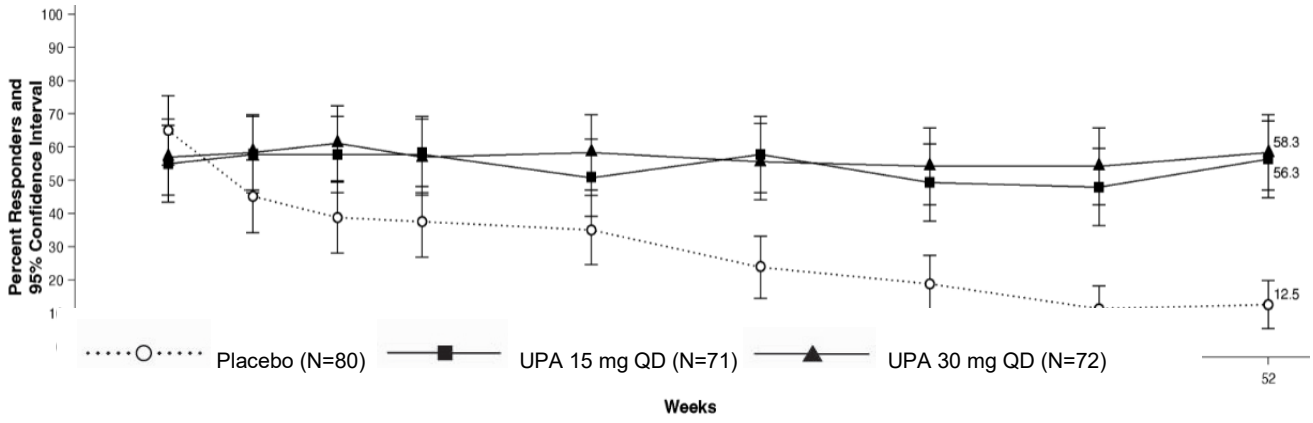
[f] ES subscore = 0

[g] ES ≤1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue)

[h] ES ≤ 1 without friability.

[i] ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue)

Figure 9. Proportion of adult patients with prior biologic failure who achieved symptomatic remission per paMS (SFS ≤ 1 and RBS = 0) over time in maintenance study UC-3



Crohn's Disease

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

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

Induction studies (CD-1 and CD-2)

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

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

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

Only study outcomes for patients with prior biologic failure will be presented below. Among these patients at baseline in CD-1 and CD-2, 34% and 44% of patients received corticosteroids, 7% and 3% of patients received immunomodulators, and 15% and 12% of patients received aminosalicylates, respectively.

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

Clinical Disease Activity and Symptoms

In CD-1 and CD-2, a significantly greater proportion of patients with prior biologic failure treated with RINVOQ 45 mg achieved the co-primary endpoint of clinical remission at Week 12 compared to placebo (Table 22). In both studies, onset of efficacy occurred as early as Week 2 compared to placebo, with a significantly greater proportion of patients treated with RINVOQ 45 mg achieving clinical response (CR-100). A significantly greater proportion of patients achieved clinical remission at Week 4 compared to placebo.

In Studies CD-1 and CD-2, a significantly greater proportion of patients with prior biologic failure treated with RINVOQ 45 mg (51% and 59%, respectively) compared to placebo (27% and 25%, respectively) achieved clinical response per CDAI at Week 12.

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

Endoscopic Assessment

In CD-1 and CD-2, a significantly greater proportion of patients with prior biologic failure treated with RINVOQ 45 mg achieved the co-primary endpoint of endoscopic response at Week 12 compared to placebo (Table 22). In CD-1 and CD-2, a greater proportion of patients with prior biologic failure treated with RINVOQ 45 mg (17% and 16%, respectively) compared to placebo (0% and 1%, respectively) achieved mucosal healing (SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at baseline) at Week 12. In CD-1 and CD-2, a greater proportion of patients with prior biologic failure treated with RINVOQ 45 mg (14% and 12%, respectively) compared to placebo (0% and 1%, respectively) achieved SES-CD 0-2.

Table 22. Proportion of Patients with Prior Biologic Failure Meeting Primary and Additional Efficacy Endpoints in Induction Studies CD-1 and CD-2

Study	CD-1 (U-EXCEED)			CD-2 (U-EXCEL)		
Treatment Group	**PBO N=171**	**UPA 45 mg N=324**	**Treatment Difference (95% CI)**	**PBO N=78**	**UPA 45 mg N=161**	**Treatment Difference (95% CI)**
Co-Primary Endpoints at Week 12						
Clinical remission[a]	14%	40%	26% (19, 33)*	14%	47%	33% (22, 44)*
Endoscopic response[b]	4%	35%	31% (25, 37)*	9%	38%	29% (19, 39)*
Additional Endpoints at Week 12						
Clinical remission per CDAI[c]	21%	39%	18% (10, 26)*	16%	44%	28% (17, 39)*
Corticosteroid-free clinical remission[a,d]	N=60 7%	N=108 37%	30% (19, 41)*	N=36 6%	N=70 39%	33% (19, 47)*
Endoscopic remission[e]	2%	19%	17% (12, 22)*	4%	21%	17% (9, 24)*

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

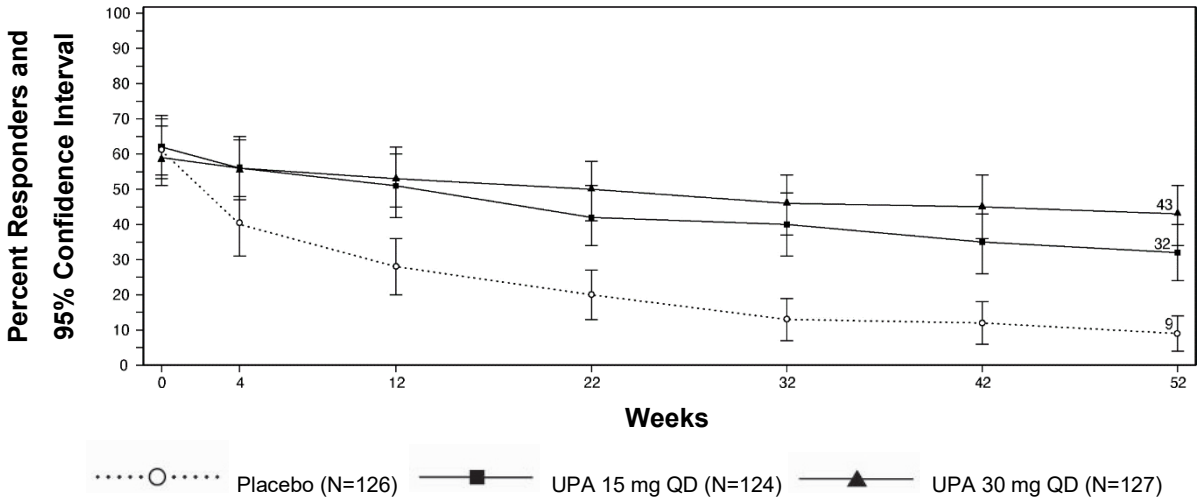
Maintenance study (CD-3)

The primary efficacy analysis for CD-3 evaluated 502 patients who achieved clinical response per SF/APS (≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily APS and neither greater than baseline) with the 12-week RINVOQ 45 mg once daily induction treatment. Patients were re-randomised to receive a maintenance regimen of either RINVOQ 15 mg or 30 mg once daily or placebo for 52 weeks, representing a total of at least 64 weeks of therapy. Of the re-randomised responders in the primary analysis, 377 patients had prior biologic failure. Only study outcomes for patients with prior biologic failure will be presented below.

Clinical disease activity and symptoms

A significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg achieved the co-primary endpoint of clinical remission per SF/APS at Week 52 compared to placebo (Figure 10, Table 23).

Figure 10 Proportion of patients with prior biologic failure achieving clinical remission in maintenance study CD-3



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

Table 23 Proportion of patients with prior biologic failure meeting primary and additional efficacy endpoints at Week 52 in maintenance study CD-3 (U-ENDURE)

Treatment Group	PBO[+] N=126	UPA 15 mg N=124	UPA 30 mg N=127	Treatment Difference 15 mg vs PBO (95% CI)	Treatment Difference 30 mg vs PBO (95% CI)
Co-Primary Endpoints					
Clinical remission[a]	9%	32%	43%	24% (14, 33)[*]	34% (24, 44)[*]
Endoscopic response[b]	4%	23%	39%	19% (11, 27)[*]	35% (26, 44)[*]
Additional Endpoints					
Clinical remission per CDAI[c]	12%	34%	45%	22% (12, 32)[*]	33% (23, 43)[*]
Corticosteroid-free clinical remission[a,d]	9%	32%	41%	24% (14, 33)[*]	32% (22, 42)[*]
Maintenance of clinical remission [a,e]	N=77 13%	N=77 44%	N=75 60%	31% (18, 45)[*]	47% (34, 60)[*]
Endoscopic remission[f]	2%	16%	27%	14% (7, 21)[*]	24% (16, 33)[*]
Deep remission [a,f,g]	2%	13%	21%	11% (4, 17)[**]	19% (11, 26) [*]

Abbreviation: PBO = placebo, UPA = upadacitinib
[+] The placebo group consisted of patients who achieved clinical response per SF/APS with RINVOQ 45 mg at the end of the induction study and were randomised to receive placebo at the start of maintenance therapy.
[*] p ≤ 0.001, UPA vs PBO comparison, adjusted treatment difference (95% CI)
[**] p ≤ 0.01, UPA vs PBO comparison, adjusted treatment difference (95% CI)

[a] Average daily very soft or liquid SF ≤ 2.8 and APS ≤ 1.0 and neither greater than baseline
[b] Decrease in SES-CD > 50% from baseline of the induction study (or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study)
[c] CDAI < 150
[d] Corticosteroid-free for 90 days prior to Week 52 and achievement of clinical remission. Among the subset of patients who were on corticosteroids at induction baseline, 35% (N=46) in RINVOQ 15 mg group, 40% (N=50) in RINVOQ 30 mg group, and 2% (N=50) in placebo were corticosteroid-free for 90 days prior to Week 52 and in clinical remission.
[e] Defined as achievement of clinical remission at Week 52 in patients who achieved clinical remission at the entry of the maintenance study.
[f] SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore >1 in any individual variable
[g] Clinical remission and endoscopic remission

Patients who were not in clinical response per SF/APS to RINVOQ induction at Week 12 in CD-1 and CD-2 received RINVOQ 30 mg once daily (122 patients) for an additional 12 weeks. Patients receiving extended treatment had longer mean disease duration (12.3 years), a higher proportion of prior biologic failure (79.5%), and more frequently failed at least 3 biologic therapies (42.3%) than the overall patient population enrolled in the induction studies. In the patients with prior biologic failure (97 patients), 23% achieved clinical remission and 54% achieved clinical response at Week 24. Of the patients who responded to the extended treatment period and continued to receive maintenance treatment with RINVOQ 30 mg, 18% achieved clinical remission and 15% achieved endoscopic response at Week 52.

Endoscopic assessments

In the patients with prior biologic failure in CD-3, a significantly greater proportion of patients treated with RINVOQ 15 mg and 30 mg achieved the co-primary endpoint of endoscopic response at Week 52 compared to placebo (Table 23). A greater proportion of patients treated with RINVOQ 15 mg and 30 mg (12% and 20%, respectively) compared to placebo (2%) achieved mucosal healing (SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥ 1 at baseline) at Week 52. A greater proportion of patients treated with RINVOQ 15 mg and 30 mg (11% and 18%, respectively) compared to placebo (2%) achieved SES-CD 0-2 at Week 52. Corticosteroid-free endoscopic remission among patients on steroid at baseline was achieved in a greater proportion of patients treated with RINVOQ 15 mg and 30 mg (15% and 24%, respectively) compared to placebo (0%) at Week 52.

Rescue treatment

In CD-3, patients who demonstrated inadequate response or lost response during maintenance were eligible to receive rescue treatment with RINVOQ 30 mg. In the patients with prior biologic failure who were randomised to RINVOQ 15 mg and received rescue treatment of RINVOQ 30 mg, 83% and 88% achieved clinical response per SF/APS and 42% and 55% achieved clinical remission 12 weeks and 24 weeks after initiating rescue, respectively. Of the patients who were randomised to placebo group

and received rescue treatment of RINVOQ 30 mg, 87% and 93% achieved clinical response per SF/APS and 52% and 55% achieved clinical remission 12 weeks and 24 weeks after initiating rescue, respectively.

Health-related and quality of life outcomes

In CD-1 and CD-2, patients treated with RINVOQ achieved greater improvement from baseline in IBDQ total score, all IBDQ domain scores including bowel symptoms, systemic symptoms, emotional function, and social function, at Week 12 compared to placebo. These improvements were maintained in patients treated with RINVOQ 15 mg and 30 mg through Week 52 in CD-3.

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% to 60%). 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, *see* Dosage/Administration).

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 (*see* Dosage/Administration).

Other Intrinsic Factors

Sex, body weight, race, age, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure.
Upadacitinib pharmacokinetics are consistent across patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, ulcerative colitis, and Crohn's disease.

Preclinical data

Repeated dose toxicity

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, at similar exposures to the expected exposure at the clinical dose of 30 mg, and at 0.9 times the expected exposure at the clinical dose of 45 mg.

Genotoxicity

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), 2 and 5 times the clinical dose of 30 mg, and 1.7 and 4 times the clinical dose of 45 mg 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, 0.8 and 7.6 times the clinical dose of 30 mg, and 0.6 and 6 times the clinical dose of 45 mg for rats and rabbits, respectively (on an AUC basis at maternal oral doses of 4 mg/kg/day or 25 mg/kg/day, respectively). Effects in rats included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and an increase in bent bones of the fore- and hind-limbs. Developmental effects in rabbits included an increase in post-implantation losses, increase in total and early resorptions, lower fetal body weights, and increased incidence of cardiac malformations. In a pre-/postnatal development study in rats, there were no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on their offspring.

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study were attributed to the developmental/teratogenic effects of upadacitinib in rats.
Following administration of upadacitinib to lactating rats, the concentrations of upadacitinib in milk over time generally paralleled those in plasma, with approximately 30-fold higher exposure in milk relative to maternal plasma. Approximately 97% of drug-related material in milk was parent drug.

Other information

Shelf life

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

Special precautions for storage

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

Authorisation number

67257 (Swissmedic)

Packs

RINVOQ 15 mg: blister with 28 prolonged-release tablets (B)
RINVOQ 30 mg: blister with 28 prolonged-release tablets (B)
RINVOQ 45 mg: blister with 28 prolonged-release tablets (B)

Marketing authorisation holder

AbbVie AG, 6330 Cham

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