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A SPECIAL MEETING REVIEW EDITION

Highlights in Crohn's Disease From Digestive Disease Week 2024

A Review of Selected Presentations From DDW 2024

May 18-21, 2024 • Washington, DC

Special Reporting on:

- Upadacitinib Treatment Is Associated With Improved Clinical and Quality of Life Outcomes in Patients With Crohn's Disease: Results From the U-ENDURE Long-Term Extension
- Risankizumab Versus Ustekinumab for the Achievement of Clinical Remission and Reduction in Inflammatory Biomarkers in Patients With Moderate-to-Severe Crohn's Disease: Results From the Phase 3b SEQUENCE Trial
- Real-World Clinical Effectiveness and Safety of Vedolizumab and Ustekinumab in Biologic-Naive Patients With Crohn's Disease by Disease Location: Results From the EVOLVE Expansion Study
- Super-Responders in Patients With Moderate-to-Severe Crohn's Disease Treated With Subcutaneous Infliximab Maintenance Therapy: A Post Hoc Analysis of the LIBERTY-CD Study
- Risankizumab Effectiveness in Ustekinumab-Naive and Ustekinumab-Experienced Patients With Crohn's Disease: Real-World Data From a Large Tertiary Center
- Improvement in Inflammatory Bowel Disease Questionnaire Items: Fatigue, Depression, Anxiety, and Bowel Urgency in Patients With Crohn's Disease Treated With Upadacitinib in Phase 3 Trials

PLUS Meeting Abstract Summaries

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RINVOQ®
upadacitinib

For moderate to severe Crohn's disease (CD) in adult TNFi-IR patients.[1]

RINVOQ helped patients achieve significant endoscopic control* and durable clinical remission.[1†]

PUT CROHN'S IN CHECK AND KEEP IT THERE

1ST & ONLY ONCE-DAILY PILL FOR MODERATE TO SEVERE CD[1,2]

Results were measured at Weeks 12 and 52[1]

U-EXCEL Induction and U-EXCEED Induction Study Design Intro: 12-week, double-blind, placebo-controlled Phase 3 induction studies that evaluated the efficacy and safety of RINVOQ in 857 adult patients (419 patients for U-EXCEED and 438 patients for U-EXCEL) with moderately to severely active Crohn's disease who demonstrated prior failure to biologic treatment (U-EXCEED) or prior failure to conventional and/or biologic treatment (U-EXCEL). Patients were randomized to receive RINVOQ 45 mg or placebo once daily for 12 weeks. The co-primary endpoints were the proportion of patients who achieved clinical remission (by CDAI) and endoscopic response (by SES-CD) at Week 12.[1]

U-ENDURE Maintenance Study Design Intro: 52-week, double-blind, placebo-controlled Phase 3 maintenance study of 343 adult patients with moderately to severely active Crohn's disease who achieved clinical response (decrease in CDAI ≥100 points from baseline from RINVOQ induction) in the U-EXCEL and U-EXCEED studies. Patients were re-randomized to receive a maintenance regimen of either RINVOQ 15 mg, RINVOQ 30 mg, or placebo once daily for 52 weeks. The co-primary endpoints were the proportion of patients who achieved clinical remission (by CDAI) and endoscopic response (by SES-CD) at Week 52.[1]

U-ENDURE Open-Label Extension Study Design Intro: Data presented at approximately 2 years is an interim analysis at 48 weeks of the U-ENDURE OLE study, which is an ongoing 240-week, open-label extension study evaluating the efficacy and safety from patients who come from the U-ENDURE Maintenance trial. Patients in this efficacy analysis were required to complete the 52-week U-ENDURE Maintenance study and received continuous RINVOQ during the Maintenance study and through Week 48 of the OLE.[3,4]

INDICATION[1]

RINVOQ is indicated for the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers.

Limitations of Use: RINVOQ is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biological therapies for Crohn's disease, or with potent immunosuppressants such as azathioprine and cyclosporine.

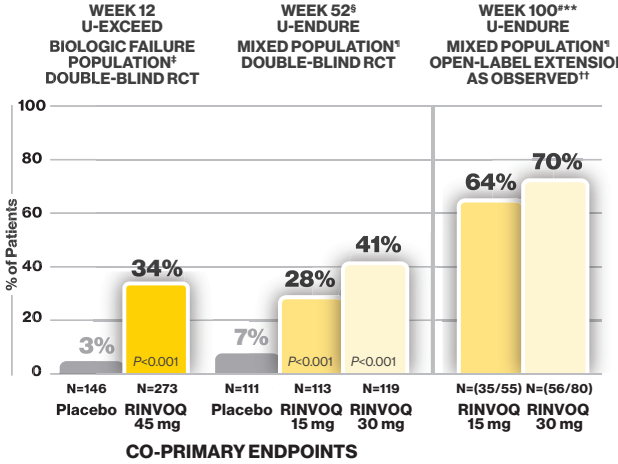
SAFETY CONSIDERATIONS[1]

Serious Infections: RINVOQ-treated patients are at increased risk of serious bacterial (including tuberculosis [TB]), fungal, viral, and opportunistic infections leading to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

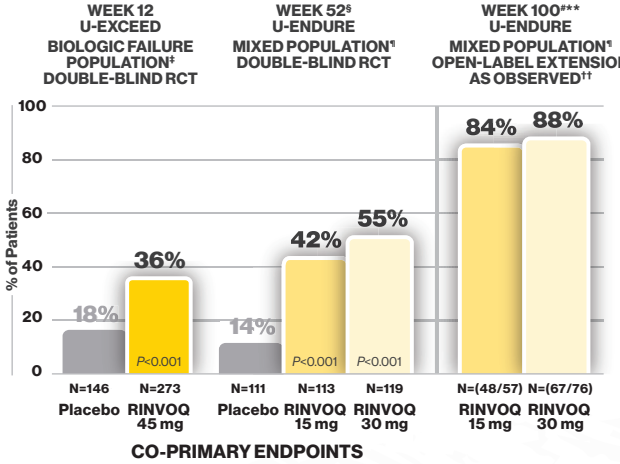
Mortality: A higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed with a Janus kinase inhibitor (JAKi) in a study comparing another JAKi with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years with ≥1 CV risk factor.

~2 YEARS OF DATA

ENDOSCOPIC RESPONSE[1,4*]



CLINICAL REMISSION[1,4†]



All *P*-values are RINVOQ treatment arms vs placebo.

RINVOQ is indicated for TNFi-IR patients.

§Results at 52 weeks are among 343 patients who achieved clinical response‖ after 12 weeks of treatment with RINVOQ in induction trials.

††Patients at Week 100 were on open-label treatment and knew the dose they were on. Data shown is an ongoing analysis and does not include all patients at Week 100 (Week 48 of OLE).[4]

RECOMMENDED MAINTENANCE DOSING

A maintenance dose of 30 mg may be considered for patients with refractory, severe, or extensive disease. Discontinue RINVOQ if an adequate therapeutic response is not achieved with the 30 mg dose.[1]

In the Open-Label Extension (OLE) analysis, the data is segmented as follows[4]:

- **RINVOQ 15 mg arm:** Patients on RINVOQ 15 mg who completed Week 52 of the U-ENDURE Maintenance trial and elected to enter the OLE period, received continuous RINVOQ 15 mg (n=76)
- **RINVOQ 30 mg arm:** Patients on RINVOQ 30 mg who completed Week 52 of the U-ENDURE Maintenance trial and elected to enter the OLE period, received continuous RINVOQ 30 mg (n=104)

#OLE LIMITATIONS:
In an OLE, there is a potential for enrichment of the long-term data in the remaining patient populations since patients who are unable to tolerate or do not respond to drug often drop out.

****AO DISCLOSURE:**
In an as observed (AO) analysis, missing visit data was excluded from calculations for that visit, which may increase the percent of responders. All observed data was used regardless of premature discontinuation of study drug, or initiation of concomitant medications. The same patient may not have a response at each timepoint.

CO-PRIMARY ENDPOINTS

Week 12 U-EXCEED: Bio-failure population‡
ENDOSCOPIC RESPONSE*: RINVOQ 34% (45 mg; n=273) vs placebo 3% (n=146), *P*<0.001
CLINICAL REMISSION†: RINVOQ 36% (45 mg; n=273) vs placebo 18% (n=146), *P*<0.001

Week 12 U-EXCEL: Mixed population¶
ENDOSCOPIC RESPONSE*: RINVOQ 46% (45 mg; n=295) vs placebo 13% (n=143), *P*<0.001
CLINICAL REMISSION†: RINVOQ 46% (45 mg; n=295) vs placebo 23% (n=143), *P*<0.001

EXPLORE THE LONG-TERM DATA
at **RINVOQHCP.COM/CD**

CDAI=Crohn's disease activity index; RCT=randomized controlled trial; SES-CD=simple endoscopic score for Crohn's disease; TNFi-IR=tumor necrosis factor inhibitor-intolerance or inadequate response.

*Endoscopic response was defined as a decrease in SES-CD >50% from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease, based on central reading. The sections evaluated on endoscopy are the rectum, sigmoid and left colon, transverse colon, right colon, and ileum (per SES-CD assessment).[1]

†Clinical remission was defined as CDAI <150 points.[1]

‡Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologics.[1]

‖Clinical response was defined as a reduction of CDAI ≥100 points from baseline.[1]

¶The mixed population included patients who had inadequate response, loss of response, or intolerance to one or more biologics (biologic failure), as well as some patients who were not bio-exposed and some patients who were bio-exposed but did not have an inadequate response, loss of response, or intolerance to biologics (bio-naïve).[1]

SAFETY CONSIDERATIONS[1] (continued)

Malignancies: Malignancies have occurred in RINVOQ-treated patients. A higher rate of lymphomas and lung cancer (in current or past smokers) was observed with another JAKi when compared with TNF blockers in RA patients.

Major Adverse Cardiovascular Events: A higher rate of CV death, myocardial infarction, and stroke was observed with a JAKi in a study comparing another JAKi with TNF blockers in RA patients ≥50 years with ≥1 CV risk factor. History of smoking increases risk.

Thrombosis: Deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. A higher rate of thrombosis was observed with another JAKi when compared with TNF blockers in RA patients.

Hypersensitivity: RINVOQ is contraindicated in patients with hypersensitivity to RINVOQ or its excipients.

Other Serious Adverse Reactions: Hypersensitivity Reactions, Gastrointestinal Perforations, Laboratory Abnormalities, and Embryo-Fetal Toxicity.

Please see additional Important Safety Information for RINVOQ, including BOXED WARNING on Serious Infections, Mortality, Malignancies, Major Adverse Cardiovascular Events, and Thrombosis, on the following page of this advertisement.

Please see Brief Summary of full Prescribing Information on adjacent pages of this advertisement.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent TB infection prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

Carefully consider the risks and benefits of treatment with RINVOQ prior to initiating therapy in patients with chronic or recurrent infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MORTALITY

In a large, randomized, postmarketing safety study comparing another Janus kinase (JAK) inhibitor with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years old with at least one cardiovascular (CV) risk factor, a higher rate of all-cause mortality, including sudden CV death, was observed with the JAK inhibitor. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ.

In a large, randomized, postmarketing safety study comparing another JAK inhibitor with TNF blockers in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]), lymphomas, and lung cancer (in current or past smokers) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk.

With RINVOQ, consider the benefits and risks for the individual patient prior to initiating or continuing therapy, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers. NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

In a large, randomized, postmarketing study comparing another JAK inhibitor with TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) was observed with the JAK inhibitor. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other CV risk factors. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing study comparing another JAK inhibitor to TNF blockers in RA patients ≥50 years old with at least one CV risk factor, a higher rate of thrombosis was observed with the JAK inhibitor. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated.

HYPERSENSITIVITY

RINVOQ is **contraindicated** in patients with known hypersensitivity to upadacitinib or any of its excipients. 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.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal (GI) perforations have been reported in clinical trials with RINVOQ. Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and patients taking NSAIDs or corticosteroids). Promptly evaluate patients presenting with new onset abdominal pain for early identification of GI perforation.

LABORATORY ABNORMALITIES

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3). Treatment with RINVOQ is not recommended in patients with an ANC <1000 cells/mm^3. Evaluate neutrophil counts at baseline and thereafter according to routine patient management.

Lymphopenia

Absolute lymphocyte counts (ALC) <500 cells/mm^3 were reported in RINVOQ-treated patients. Treatment with RINVOQ is not recommended in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Anemia

Decreases in hemoglobin levels to <8 g/dL were reported in RINVOQ-treated patients. Treatment should not be initiated or should be interrupted in patients with hemoglobin levels <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

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. Manage patients according to clinical guidelines for the management of hyperlipidemia. Evaluate patients 12 weeks after initiation of treatment and thereafter according to the clinical guidelines for hyperlipidemia.

Liver enzyme 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 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

EMBRYO-FETAL TOXICITY

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose. Verify pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ.

VACCINATION

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, patients should be brought up to date on all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

MEDICATION RESIDUE IN STOOL

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic or functional GI conditions with shortened GI 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.

LACTATION

There are no data on the presence of RINVOQ in human milk, the effects on the breastfed infant, or the effects on milk production. Available data in animals have shown the excretion of RINVOQ in milk. Advise patients that breastfeeding is not recommended during treatment with RINVOQ and for 6 days after the last dose.

HEPATIC IMPAIRMENT

RINVOQ is not recommended for use in patients with severe hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions in RINVOQ clinical trials were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, headache, increased blood creatine phosphokinase, hypersensitivity, folliculitis, abdominal pain, increased weight, influenza, fatigue, neutropenia, myalgia, influenza-like illness, elevated liver enzymes, rash, and anemia.

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ.

Dosage Forms and Strengths: RINVOQ is available in 15 mg, 30 mg, and 45 mg extended-release tablets.

Please see Brief Summary of full Prescribing Information on adjacent pages of this advertisement.

References: 1. RINVOQ [package insert]. North Chicago, IL: AbbVie Inc.; 2024. **2.** Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. *Nat Rev Dis Primers*. 2020;6(1):22. **3.** Data on File. ABVRRTI77657. **4.** Data on File. ABVRRTI78550.

abbvie

RINVOQ®
upadacitinib

RINVOQ® (RIN-VOKE) (upadacitinib) extended-release tablets, for oral use

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, and THROMBOSIS

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions, Adverse Reactions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt RINVOQ until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with RINVOQ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions]*.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke *[see Warnings and Precautions]*.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

RINVOQ® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine.

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 or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for Crohn's disease, or with potent immunosuppressants such as azathioprine and cyclosporine.

CONTRAINDICATIONS

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions]*. 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 infection
- 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

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RINVOQ. RINVOQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions]*. 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 trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

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 TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen.

Major Adverse Cardiovascular Events

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 major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.

Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death.

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, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ and be evaluated promptly and treated appropriately. Avoid RINVOQ in patients that may be at increased risk of thrombosis.

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 Adverse Reactions]*.

Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ *[see Adverse Reactions]*.

Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and those taking concomitant medications including NSAIDs or corticosteroids). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation and interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3).

Lymphopenia

ALC less than 500 cells/mm^3 were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3).

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL).

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 Adverse Reactions]*. 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.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes 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.

Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations]*.

Vaccinations

Avoid use of live vaccines during or immediately prior to RINVOQ therapy initiation. Prior to initiating RINVOQ treatment, it is recommended that patients be brought up to date with all immunizations, including prophylactic varicella zoster or herpes zoster vaccinations, in agreement with current immunization guidelines.

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.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions]*
- Mortality *[see Warnings and Precautions]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions]*
- Thrombosis *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Gastrointestinal Perforations *[see Warnings and Precautions]*
- Laboratory Abnormalities *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Patients with Rheumatoid Arthritis

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the Phase 3 clinical trials of whom 2806 were exposed for at least one year.

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the trial design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In trials RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

Table 1: Adverse Reactions Reported in ≥ 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Trials

Adverse Reaction	Placebo	RINVOQ 15 mg
	N = 1042 (%)	N = 1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

Placebo-controlled Trials: Trials RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Trials RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), and upadacitinib 30 mg (n=384). Trial RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling trials RA-III and RA-V.

MTX-controlled Trials: Trials RA-I and RA-II were integrated to represent safety through 12/14 weeks for MTX (n=530), RINVOQ 15 mg (n=534), and upadacitinib 30 mg (n=529).

12-Month Exposure Dataset: Trials RA-I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n=1213) and upadacitinib 30 mg (n=1203).

Exposure adjusted incidence rates were adjusted by trial for all the adverse events reported in this section.

Specific Adverse Reactions

Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

Serious Infections

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

Placebo-controlled Trials and MTX-controlled Trials: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

Opportunistic Infections (excluding tuberculosis)

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

Malignancies

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

Gastrointestinal Perforations

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

Thrombosis

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) 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, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

Creatine Phosphokinase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related 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. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related 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 RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related 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. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

RINVOQ was studied up to 8 weeks in patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled induction studies (UC-1, UC-2) and a randomized, double-blind, placebo controlled, dose-finding study (UC-4; NCT02819635). Long term safety up to 52-weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-3) and a long-term extension study.

In the two induction studies (UC-1, UC-2) and a dose finding study (UC-4), 1097 patients were enrolled of whom 719 patients received RINVOQ 45 mg once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg once daily and 251 patients received RINVOQ 30 mg once daily.

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 2 and 3, respectively.

Table 2: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (UC-1, UC-2 and UC-4)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N = 378 (%)	N = 719 (%)
Upper respiratory tract infection*	7	9
Acne*	1	6
Increased blood creatine phosphokinase	1	5
Neutropenia*	<1	5
Rash*	1	4
Elevated liver enzymes**	2	3
Lymphopenia*	1	3
Folliculitis	1	2
Herpes simplex*	<1	2

* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury and cholestasis.

Other adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

Table 3: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	N = 245 (%)	N = 250 (%)	N = 251 (%)
Upper respiratory tract infection*	18	16	20
Increased blood creatine phosphokinase	2	6	8
Neutropenia*	2	3	6
Elevated liver enzymes**	1	6	4
Rash*	4	5	5
Herpes zoster	0	4	4
Folliculitis	2	2	4
Hypercholesterolemia*	1	2	4
Influenza	1	3	3
Herpes simplex*	1	2	3
Lymphopenia*	2	3	2
Hyperlipidemia*	0	2	2

[1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily
* Composed of several similar terms
** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury, and cholestasis.

The adverse reaction of non-melanoma skin cancer was reported in 1% of patients in the RINVOQ 30 mg group and none of the patients in the RINVOQ 15 mg or placebo group through Week 52.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Overall, the safety profile observed in patients with ulcerative colitis treated with RINVOQ was generally similar to the safety profile in patients with RA and AD.

Specific Adverse Reactions

Serious Infections

Induction Studies: In UC-1, UC-2, and UC-4, serious infections were reported in 5 patients (8.4 per 100 patient-years) treated with placebo and 9 patients (8.4 per 100 patient-years) treated with RINVOQ 45 mg through 8 weeks.

Placebo-controlled Maintenance Study: In UC-3, serious infections were reported in 8 patients (6.3 per 100 patient-years) treated with placebo, 8 patients (4.5 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (3.1 per 100 patient-years) treated with RINVOQ 30 mg through 52 weeks.

Laboratory Abnormalities

Hepatic Transaminase Elevations

In studies UC-1, UC-2, and UC-4, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 1.5% of patients treated with RINVOQ 45 mg, and 0% of patients treated with placebo for 8 weeks. AST elevations to ≥ 3 x ULN occurred in 1.5% of patients treated with RINVOQ 45 mg, and 0.3% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN occurred in 0.4% of patients treated with RINVOQ 45 mg and 0% of patients treated with placebo.

In UC-3, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 4% of patients treated with RINVOQ 30 mg, 2% of patients treated with RINVOQ 15 mg, and 0.8% of patients treated with placebo for 52 weeks. Elevations of AST to ≥ 3 x ULN in at least one measurement were observed in 2% of patients treated with RINVOQ 30 mg, 1.6% of patients treated with RINVOQ 15 mg and 0.4% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN were observed in 0.8% of patients treated with 30 mg, 0.4% of patients treated with 15 mg, and 0.4% of patients treated with placebo.

Overall, laboratory abnormalities observed in patients with ulcerative colitis treated with RINVOQ were similar to those described in patients with RA.

Adverse Reactions in Patients with Crohn's Disease

RINVOQ was studied up to 12 weeks in patients with moderately to severely active CD in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2). Long term safety up to 52 weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3), with additional data provided from a long-term extension (LTE) period.

In the two induction studies (CD-1, CD-2), 1021 patients were enrolled, of whom 674 patients received RINVOQ 45 mg once daily during the placebo-controlled period.

In the maintenance study (CD-3), 673 patients were enrolled, of whom 221 patients received RINVOQ 15 mg once daily and 229 patients received RINVOQ 30 mg once daily during the randomized, placebo-controlled period.

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

Adverse reactions reported in ≥2% of patients treated with RINVOQ and at a higher rate than placebo in the induction and maintenance studies are shown in Tables 4 and 5, respectively.

Table 4: Adverse Reactions Reported in ≥2% of Patients with Crohn's Disease Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (CD-1 and CD-2)

Adverse Reaction	Placebo	RINVOQ 45 mg Once Daily
	N = 347 (%)	N = 674 (%)
Upper respiratory tract infection*	8	13
Anemia*	6	7
Acne*	2	6
Pyrexia	3	4
Increased blood creatine phosphokinase	1	3
Influenza	1	3
Herpes simplex*	1	3
Leukopenia*	1	2
Neutropenia*	<1	2
Herpes zoster	0	2
* Composed of several similar terms		

Adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 12 included folliculitis, hypercholesterolemia, bronchitis, pneumonia, oral candidiasis, and hyperlipidemia.

Table 5: Adverse Reactions Reported in ≥2% of Patients with Crohn's Disease Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (CD-3)[1]

Adverse Reaction	Placebo	RINVOQ 15 mg Once Daily	RINVOQ 30 mg Once Daily
	N = 223 (%)	N = 221 (%)	N = 229 (%)
Upper respiratory tract infection*	11	14	12
Pyrexia	2	3	7
Herpes zoster*	2	3	5
Headache*	1	3	5
Acne*	3	2	5
Gastroenteritis*	2	3	3
Fatigue	2	3	3
Increased blood creatine phosphokinase	1	2	3
Elevated liver enzymes[2]	<1	2	3
Leukopenia*	<1	1	2
Neutropenia*	<1	1	2
Bronchitis*	0	1	2
Pneumonia*	1	4	1
Cough	2	3	1

[1] Patients who were responders to 12 weeks induction therapy with RINVOQ 45 mg once daily.
[2] Elevated liver enzymes includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, transaminases increased, blood bilirubin increased.
* Composed of several similar terms

Adverse reactions reported in less than 2% of patients in the RINVOQ 15 mg or 30 mg group and at a higher rate than in the placebo group through Week 52 included hyperlipidemia, oral candidiasis, and hypercholesterolemia.

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Specific Adverse Reactions

Serious Infections

Induction Studies: In CD-1 and CD-2, serious infections were reported in 6 patients (8 per 100 patient-years) treated with placebo and 13 patients (9 per 100 patient-years) treated with RINVOQ 45 mg through 12 weeks of the placebo-controlled period.

Maintenance Study/LTE: In the long-term placebo-controlled period, serious infections were reported in 10 patients (7 per 100 patient-years) treated with placebo, 7 patients (4 per 100 patient-years) treated with RINVOQ 15 mg, and 13 patients (6 per 100 patient-years) treated with RINVOQ 30 mg.

Gastrointestinal Perforations

Induction Studies: During the induction studies in all patients treated with RINVOQ 45 mg (N=938), gastrointestinal perforation was reported in 4 patients (2 per 100 patient-years). In the placebo-controlled induction period, in CD-1 and CD-2, gastrointestinal perforation was reported in no patients treated with placebo (N=347) and 1 patient (1 per 100 patient-years) treated with RINVOQ 45 mg (N=674) through 12 weeks.

Maintenance Study/LTE: In the long-term placebo-controlled period, gastrointestinal perforation was reported in 1 patient (1 per 100 patient-years) treated with placebo, 1 patient (<1 per 100 patient-years) treated with RINVOQ 15 mg, and 1 patient (<1 per 100 patient-years) treated with RINVOQ 30 mg.

Patients who received placebo or RINVOQ 15 mg for maintenance therapy and lost response were treated with rescue RINVOQ 30 mg (N=336). Among these patients, gastrointestinal perforation was reported in 3 patients (1 per 100 patient-years) through long-term treatment.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when RINVOQ is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole, clarithromycin, and grapefruit), which may increase the risk of RINVOQ adverse reactions. Monitor patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondylarthritis closely for adverse reactions when co-administering RINVOQ 15 mg once daily with strong CYP3A4 inhibitors. Food or drink containing grapefruit should be avoided during treatment with RINVOQ.

For patients with atopic dermatitis, coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

For patients with ulcerative colitis or Crohn's disease taking strong CYP3A4 inhibitors, reduce the RINVOQ induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when RINVOQ is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Surveillance Program

There is a pregnancy surveillance program for RINVOQ that monitors pregnancy outcomes in women exposed to RINVOQ. If RINVOQ exposure occurs during pregnancy, healthcare providers or patients should report the pregnancy by calling 1-800-633-9110.

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15 mg dose, 0.8 and 7.6 times the 30 mg dose, and 0.6 and 5.6 times the maximum recommended human dose (MRHD) of 45 mg (on an AUC basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at exposures approximately 0.29 and 2.2 times the 15 mg dose, 0.15 times and 1.1 times the 30 mg dose, and at 0.11 and 0.82 times the MRHD (on an AUC basis). In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and the same as the MRHD (on an AUC basis) resulted in no maternal or developmental toxicity (*see Data).*

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or inflammatory bowel disease. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the 15 mg dose, 0.9 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the 15 mg dose, 43 times the 30 mg dose, and 31 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the 15 mg dose, 0.8 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.29 times the 15 mg dose, 0.15 times the 30 mg dose, and 0.11 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the 15 mg dose, 7.6 times the 30 mg dose, and 5.6 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2.2 times the 15 mg dose, 1.1 times the 30 mg dose, and 0.82 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and at approximately the same exposure as the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on AUC_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations].*

Contraception

Females

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations].* Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

Pediatric Use

Ulcerative Colitis and Crohn's Disease

The safety and effectiveness of RINVOQ in pediatric patients with ulcerative colitis and Crohn's disease have not been established.

Geriatric Use

Ulcerative Colitis

Of the 1097 patients treated in the controlled clinical trials, a total of 95 patients with ulcerative colitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ulcerative colitis to determine whether they respond differently from younger adult patients.

Crohn's Disease

Of the 1021 patients who were treated in the controlled induction clinical trials, a total of 39 patients with Crohn's disease were 65 years of age or older, and no patients were 75 years of age or older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with Crohn's disease to determine whether they respond differently from younger adult patients.

Renal Impairment

For patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis, no dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73 m^2), moderate (eGFR 30 to < 60 mL/min/1.73 m^2), or severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2).

For patients with atopic dermatitis, the maximum recommended dosage is 15 mg once daily for patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment.

For patients with ulcerative colitis or Crohn's disease, the recommended dosage for severe renal impairment is 30 mg once daily for induction and 15 mg once daily for maintenance. No dosage adjustment is needed in patients with mild or moderate renal impairment.

RINVOQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73m^2). Use in patients with atopic dermatitis, ulcerative colitis, or Crohn's disease with end stage renal disease is not recommended.

Hepatic Impairment

The use of RINVOQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and therefore not recommended for use in patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis no dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

For patients with ulcerative colitis or Crohn's disease, the recommended dosage for mild to moderate hepatic impairment is 30 mg once daily for induction and 15 mg once daily for maintenance.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the 15 mg dose, 2 and 5 times the 30 mg dose, and 1.6 and 4 times the maximum recommended human dose (MRHD) of 45 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negative in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 42 and 84 times the 15 mg dose, 22 and 43 times the 30 mg dose, and 16 and 31 times the MRHD, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the 15 mg dose, 11 and 43 times the 30 mg dose, and 8 and 31 times the MRHD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the 15 mg dose, 0.9 times the 30 mg dose, and at 0.6 times the MRHD on an AUC basis).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions]*.

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ.

Advise patients that exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions]*.

Major Adverse Cardiovascular Events

Inform patients that RINVOQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions]*.

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions]*.

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions]*.

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDs, corticosteroids, or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions]*.

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ *[see Adverse Reactions]*.

Laboratory Abnormalities

Inform patients that RINVOQ may affect certain lab tests, and that blood tests are required before and during RINVOQ treatment *[see Warnings and Precautions]*.

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ prior to a potential vaccination *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions and Use in Specific Populations]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations]*.

Advise women exposed to RINVOQ during pregnancy that there is a pregnancy surveillance program that monitors pregnancy outcomes *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with RINVOQ and for 6 days after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients not to chew, crush, or split RINVOQ tablets.

Advise patients to avoid food or drink containing grapefruit during treatment with RINVOQ *[see Drug Interactions]*.

Medication Residue in Stool

Instruct patients to notify their healthcare provider if they repeatedly notice medication residue (e.g., intact RINVOQ tablet or fragments) in stool or ostomy output *[see Warnings and Precautions]*.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, USA

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Upadacitinib Treatment Is Associated With Improved Clinical and Quality of Life Outcomes in Patients With Crohn's Disease: Results From the U-ENDURE Long-Term Extension

The oral selective Janus kinase inhibitor upadacitinib received US Food and Drug Administration (FDA) approval for the treatment of adults with moderately to severely active Crohn's disease (CD) who had an inadequate response or intolerance to 1 or more tumor necrosis factor (TNF) blockers based on 2 placebo-controlled phase 3 induction trials (U-EXCEL and U-EXCEED) and a maintenance trial (U-ENDURE).[1,2] In those trials, upadacitinib was significantly more effective than placebo in patients with moderate-to-severe CD as assessed by clinical remission rate and endoscopic response rate.

In U-ENDURE, upadacitinib maintenance therapy at 15 mg or 30 mg once daily was associated with improvements in clinical response/remission, health-related quality of life (HRQOL), and reductions in fatigue compared with maintenance placebo in patients responding to upadacitinib induction.[2] Patients who completed the 52-week maintenance period in U-ENDURE could continue treatment in a long-term extension (LTE) study.

At DDW 2024, a long-term analysis of the efficacy and safety of upadacitinib versus placebo was reported.[3] The analysis included randomized responders (patients from week 0 of the maintenance substudy 1) and patients in the ongoing U-ENDURE LTE study.[3] Efficacy and health-related outcomes were assessed in patients in the LTE who were receiving upadacitinib 15 mg (n=107), upadacitinib 30 mg (n=173), or placebo (n=89) once daily.

The LTE showed sustained improvements in clinical remission rates and HRQOL outcomes with upadacitinib versus placebo (Figure 1). Week 48 stool frequency/abdominal pain score (SF/APS) clinical remission rates were 76.7% with upadacitinib 30 mg, 82.1% with upadacitinib 15 mg, and 70.2% with placebo, and week 48 Crohn's Disease Activity Index (CDAI) clinical remission rates were 84.3%, 82.3%, and 75.4%, respectively. Regarding HRQOL, week 48 IBD Questionnaire (IBDQ) response rates were 94.0% with upadacitinib 30 mg, 88.2% with upadacitinib 15 mg, and 78.8% with placebo, and changes in Functional Assessment of Chronic Illness Therapy–Fatigue from induction were also greater with upadacitinib versus placebo.

Researchers noted that comparable clinical and QOL outcomes were observed in patients from cohort 1 and in patients meeting the criteria for moderately to severely active CD,

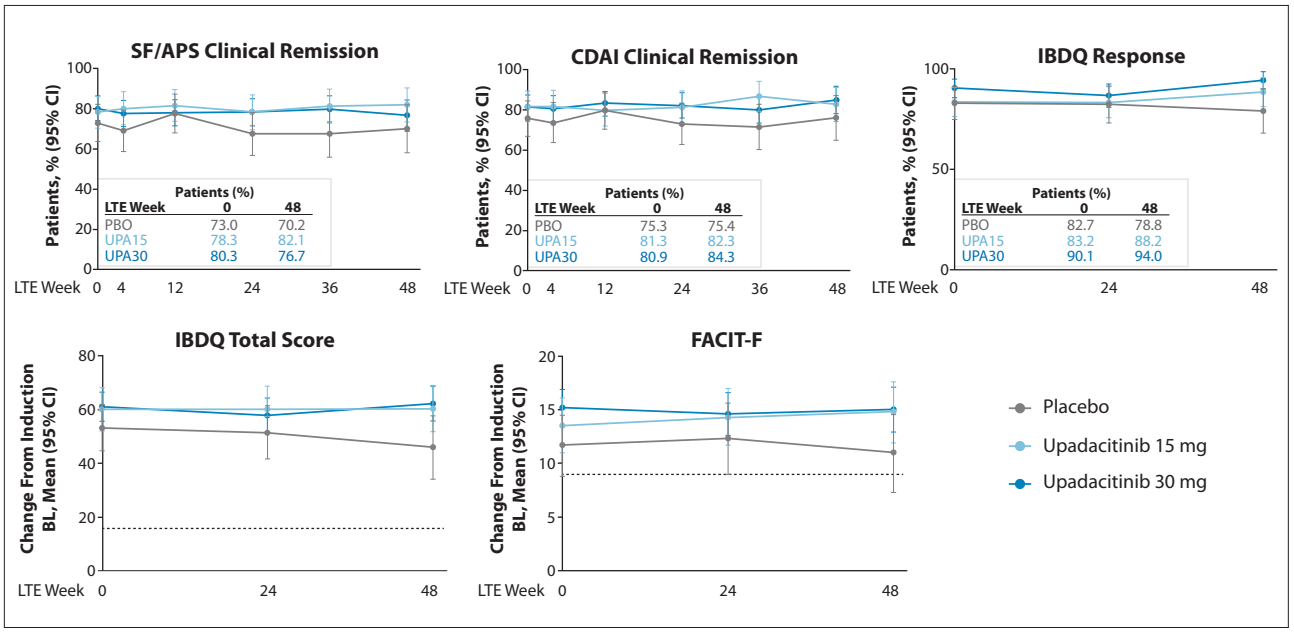

Figure 1. Clinical and quality of life outcomes through 48 weeks of the LTE (as-observed) with upadacitinib in patients with Crohn's disease: results from the U-ENDURE long-term extension. APS, abdominal pain score; BL, baseline; CDAI, Crohn's Disease Activity Index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; LTE, long-term extension; PBO, placebo; SF, stool frequency; UPA15, upadacitinib 15 mg; UPA30, upadacitinib 30 mg. Adapted from Rubin et al. Abstract Su1798. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

> Improvements in fatigue and quality of life are prioritized by our patients with CD. It is reassuring that benefits related to quality of life are as durable as those associated with symptoms with advanced therapies such as Janus kinase inhibitors in patients with CD.
> —Millie D. Long, MD, MPH

defined as a CDAI ≥200 at induction baseline and clinical response at week 12 with upadacitinib.

A safety analysis was conducted that included the LTE and randomized responders, with patients having received upadacitinib 30 mg for a median of 96.0 weeks, upadacitinib 15 mg for a median of 51.6 weeks, or placebo for a median of 20 weeks. Rates of some adverse events (AEs) were numerically higher with upadacitinib, including herpes zoster, adjudicated gastrointestinal perforations, neutropenia, lymphopenia, creatine phosphokinase elevation, and hepatic disorders. However, no new safety outcomes were observed during the LTE.

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3.Rubin DT, Louis E, Panes J, et al. Upadacitinib treatment is associated with improved clinical and quality of life outcomes in patients with Crohn's disease: results from the U-ENDURE long-term extension. Abstract Su1798. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

Risankizumab Versus Ustekinumab for the Achievement of Clinical Remission and Reduction in Inflammatory Biomarkers in Patients With Moderate-to-Severe Crohn's Disease: Results From the Phase 3b SEQUENCE Trial

The open-label, multicenter, randomized, phase 3b SEQUENCE trial compared the selective interleukin (IL)-23 p19 inhibitor risankizumab against the IL-12/IL-23 p40 inhibitor ustekinumab in patients with moderate-to-severe CD refractory to anti-TNF therapy. A total of 520 patients received either risankizumab 600 mg intravenous (IV) induction at baseline, week 4, and week 8, followed by 360 mg subcutaneous (SC) maintenance dosing every 8 weeks starting at week 12 (n=255), or ustekinumab administered via a single IV weight-based dose followed by ustekinumab 90 mg SC maintenance dosing every 8 weeks starting at week 8 (n=265). A corticosteroid taper was started at week 2. Patients were stratified based on number of anti-TNF therapies failed and steroid use at baseline.

As presented at the United European Gastroenterology Week 2023, the trial met its 2 primary endpoints, demonstrating noninferiority in week

ABSTRACT SUMMARY One-Year Safety and Effectiveness of Ustekinumab in Patients With Crohn's Disease: The K-STAR Study

The K-STAR study prospectively evaluated the safety and effectiveness of ustekinumab in 457 Korean patients with CD, 53.4% of whom had received prior biologics (Abstract Mo1855). At the week 52-66 visit, clinical response and clinical remission rates were 62.4% and 52.6%, respectively, in the overall population; 60.3% and 53.8%, respectively, in biologic-naive patients; and 64.0% and 51.3%, respectively, in biologic-experienced patients. Endoscopic response and remission rates were 29.4% and 29.2% overall, 50.0% and 40.0% in biologic-naive patients, and 0% and 11.1% in biologic-experienced patients, respectively. Factors inversely associated with clinical remission included colonic involvement (OR, 0.32; *P*=.028), ileocolonic involvement (OR, 0.45; *P*=.021), baseline CRP level (OR, 0.90; *P*=.009), and exposure to at least 2 biologics (OR, 0.38; *P*=.003). The incidence of SAEs was 26.6 per 100 PY; no serious infections were reported.

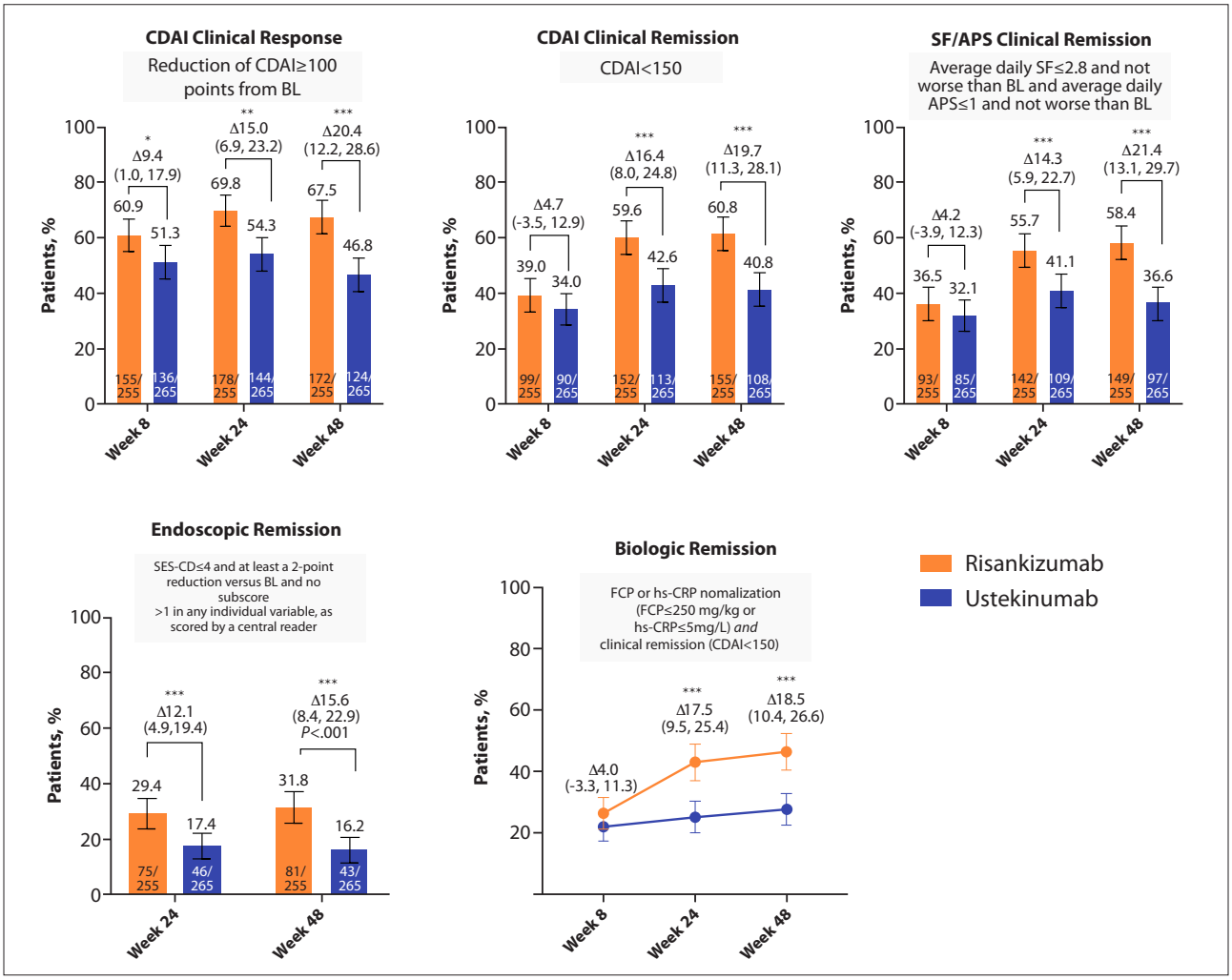

Figure 2. Remission in patients with moderate-to-severe Crohn's disease with risankizumab versus ustekinumab: results from the phase 3b SEQUENCE trial. Δ, adjusted treatment difference; APS, abdominal pain score; BL, baseline; CD, Crohn's disease; CDAI, CD Activity Index; FCP, fecal calprotectin; hs-CRP, high sensitivity C-reactive protein; SES-CD, Simple Endoscopic Score for CD; SF, stool frequency. **P*≤.05; ***P*≤.01; ****P*≤.001. Adapted from Dubinsky et al. Oral Presentation 763. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

24 clinical remission rate (CDAI <150) with risankizumab versus ustekinumab in approximately one-half of planned subjects (58.6% vs 39.5%) and significantly superior endoscopic remission rate, defined as a Simple Endoscopic Score for CD (SES-CD) less than or equal to 4 at week 48 with risankizumab versus ustekinumab (31.8% vs 16.2%; *P*<.0001).[1]

At DDW 2024, an update was presented from SEQUENCE reporting on changes in biomarkers including C-reactive protein (CRP) and fecal calprotectin (FCP), clinical responses, clinical remissions, and biologic remissions (Figure 2).[2] The CDAI clinical response rate, defined as a reduction of CDAI by at least 100 points from baseline, was significantly higher with risankizumab versus ustekinumab starting at week 8 (60.9% vs 51.3%; *P*≤.05) (a post hoc analysis) and continuing through week 48 (67.5% vs 46.8%; *P*≤.001) (a prespecified analysis).

The clinical remission rate (CDAI <150) was also significantly higher with risankizumab versus ustekinumab starting at week 24 (59.6% vs 42.6%; *P*≤.001) and continuing through week 48 (60.8% vs 40.8%; *P*≤.001). Clinical remission rates assessed by SF/APS were also significantly higher at weeks 24 and 48 in the risankizumab arm.

Endoscopic remission rates with risankizumab were nearly twice those with ustekinumab, as previously reported (31.8% vs 16.2%; *P*<.001). Mucosal healing, defined as an SES-CD ulcerated surface subscore of 0 in patients with a subscore of at least 1 at baseline, was attained in 30.2% of patients receiving risankizumab and 12.1% of patients receiving ustekinumab (*P*≤.001).

Regarding biomarkers, risankizumab was associated with significantly

greater reductions from baseline over ustekinumab in high-sensitivity CRP starting at week 8 and in FCP starting at week 24, with sustained reductions through week 48.

Finally, rates of biologic remission, defined as normalization of FCP (≤250 mg/kg) or high-sensitivity CRP (≤5 mg/L) and clinical remission, were also significantly superior with risankizumab versus ustekinumab at week 24 (17.5% difference between arms; $P \leq .001$) and at week 48 (18.5% difference between arms; $P \leq .001$).

The authors concluded that, in this randomized trial of patients with CD for whom prior anti-TNF therapy had failed, risankizumab was associated with significant benefits over ustekinumab related to the short-term and long-term treatment goals of symptomatic and endoscopic improvement as recommended by the STRIDE-II,[3] as well as in the intermediate goal of inflammatory biomarker reduction and in the composite endpoint of biologic remission.

Head-to-head treat-through trials in CD with objective, biologic outcomes are needed to guide positioning. SEQUENCE trial is, therefore, extremely relevant for clinical care. In this trial, a greater percentage of anti-TNF therapy-experienced patients with CD achieved biologic remission on risankizumab as compared to ustekinumab. This speaks to a potentially differential effect of the IL-23 mechanism in anti-TNF therapy-exposed patients with CD.
—Millie D. Long, MD, MPH

References

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Real-World Clinical Effectiveness and Safety of Vedolizumab and Ustekinumab in Biologic-Naive Patients With Crohn's Disease by Disease Location: Results From the EVOLVE Expansion Study

Two biologics currently approved for the treatment of patients with moderately to severely active CD are the α4β7 integrin antibody vedolizumab and the IL-12/IL-23 p40 inhibitor ustekinumab.[1,2] The real-world retrospective, observational, multicenter EVOLVE expansion trial used patient charts to compare safety and efficacy outcomes in patients with CD receiving vedolizumab or ustekinumab.[3] The study enrolled patients with CD in Australia, Belgium, and Switzerland who were biologic-naive, had initiated treatment with vedolizumab or ustekinumab, and had at least 6 months of follow-up.

An analysis from EVOLVE presented at DDW 2024 reported on the real-world clinical effectiveness and safety of vedolizumab and ustekinumab based on disease location. The analysis included 293 patients with ileal CD (158 receiving vedolizumab and 135 receiving ustekinumab), 185 patients with ileocolonic CD (91 receiving vedolizumab and 94 receiving ustekinumab), and 121 patients with colonic CD (84 receiving vedolizumab and 37 receiving ustekinumab). Significant differences in some baseline characteristics were noted between the vedolizumab and ustekinumab groups. Although the differences that reached significance varied by disease location subgroup, factors that were significantly different in at least 1 subgroup included age, country, year of treatment initiation, corticosteroid dependency status, and biochemical index.

After an inverse probability of treatment weighting method was used to adjust for differences in baseline characteristics between groups, demographic and baseline clinical characteristics were similar between treatment groups across disease location subgroups.

During 36 months of treatment, there was no significant difference in the cumulative rate of clinical response with vedolizumab versus ustekinumab in patients with ileal CD (79.2% vs 85.8%; $P = .67$), ileoco-

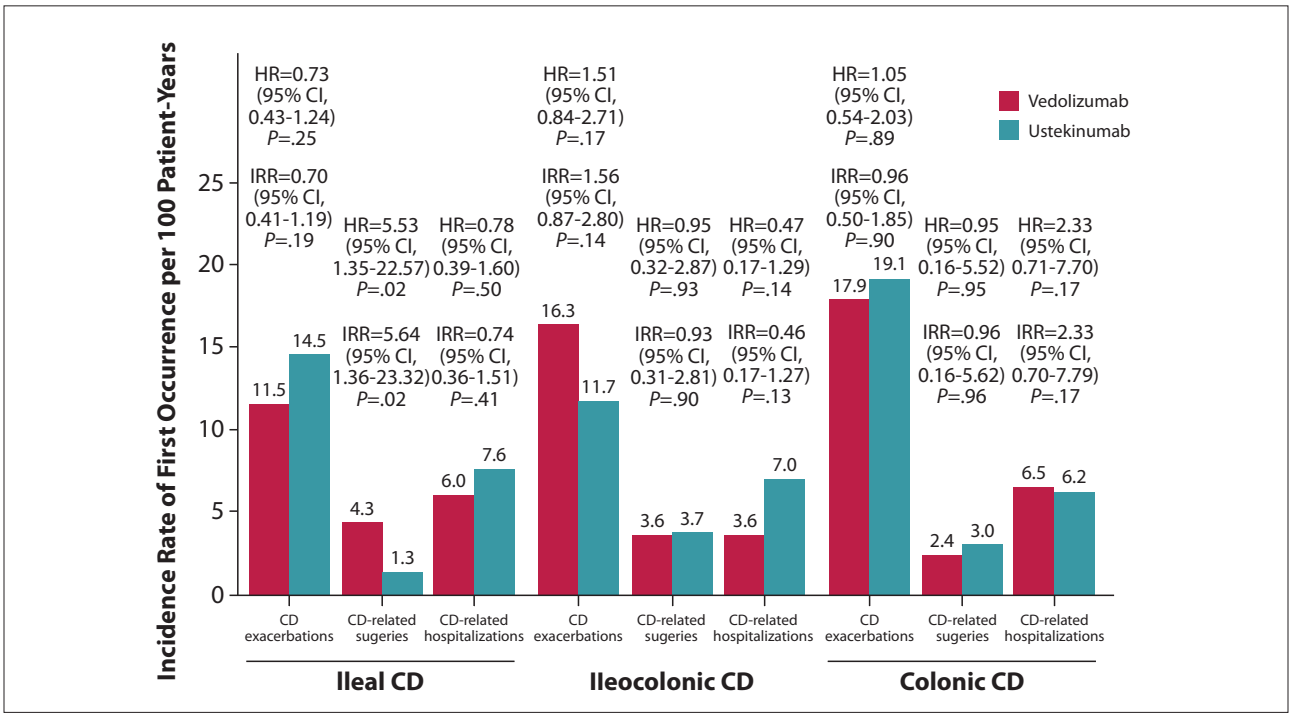

Figure 3. CD exacerbations, CD-related surgeries, and CD-related hospitalizations in patients with ileal, ileocolonic, and colonic CD who initiated treatment with vedolizumab or ustekinumab: results from the EVOLVE expansion study. CD, Crohn's disease; HR, hazard ratio; IRR, incidence rate ratio. Adapted from Scharl et al. Abstract Tu1821. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

lonic CD (85.7% vs 90.8%; *P*=.94), and colonic CD (88.0% vs 68.0%; *P*=.22). Similarly, there were no significant differences between treatment groups in the cumulative rate of clinical remission, mucosal health, and treatment persistence.

The incidence of serious AEs (SAEs) was similar in the vedolizumab and ustekinumab groups in patients with ileal CD (5.2 vs 4.6 events per 100 patient-years [PY]; *P*=.83) and ileocolonic CD (3.6 vs 5.7 events per 100 PY; *P*=.37), and higher in the vedolizumab group versus the ustekinumab group in patients with colonic CD (8.4 vs 8.1 events per 100 PY; *P*=.04).

Serious infections occurred at a similar rate in the vedolizumab and ustekinumab groups in patients with ileal CD (1.4 vs 0.4 events per 100 PY; *P*=.36) and were more frequent with vedolizumab versus ustekinumab in patients with ileocolonic CD (1.2 vs 0 events per 100 PY; *P* value not estimable) and in patients with colonic CD (1.8 vs 1.5 events per 100 PY; *P*=.03). Both SAEs and serious infections occurred at similar rates across disease location subgroups.

Rates of CD exacerbations were similar between treatment groups in all disease location subgroups and were also similar across disease location subgroups (Figure 3). Among patients with ileal CD, rates of

ABSTRACT SUMMARY Long-Term Efficacy and Safety of Risankizumab in Patients With Moderate-to-Severe Crohn's Disease With Up to 3 Years of Treatment: Results From the FORTIFY Open-Label Long-Term Extension

FORTIFY is an open-label extension study evaluating the long-term efficacy and safety of risankizumab in patients with moderate-to-severe CD. At DDW 2024, a post hoc analysis was presented of patients enrolled in the open-label extension who had attained a CDAI clinical response at the time of starting maintenance therapy with risankizumab SC every 8 weeks at 180 mg (n=753) or 360 mg (n=203) (Abstract Su1761). Overall, clinical response and clinical remission rates remained stable through 152 weeks. In a pooled analysis, week 152 CDAI clinical response and clinical remission rates were 91.8% and 81.6%, respectively and the SF/APS clinical remission rate was 75.2%. Week 152 endoscopic response and remission rates were 75.8% and 61.1%, respectively, and 51.9% of patients had an ulcer-free endoscopy. SAEs occurred at a rate of 12.2 per 100 PY and serious infections occurred at a rate of 1.9 per 100 PY. No active tuberculosis events were reported. The rate of hypersensitivity events was 4.2 per 100 PY; no serious hypersensitivity or anaphylactic reactions occurred.

A number of factors weigh into therapy selection: comorbidities, extra-intestinal manifestations, disease location and phenotype, and prior treatments. In my practice, ileal disease can be difficult to heal. This study showed an increased risk of CD-related surgery among those with ileal disease on vedolizumab as compared to ustekinumab.
—Millie D. Long, MD, MPH

CD-related surgeries were higher in the vedolizumab group than in the ustekinumab group (4.3 vs 1.3 events per 100 PY; hazard ratio, 5.53; *P*=.02). However, only 12 of 158 patients with ileal CD receiving vedolizumab (7.6%) and 3 of 135 patients receiving ustekinumab (2.2%) required surgery, indicating that surgery rates were low in both groups. No other differences in CD-related surgery rates were noted. Finally, there were no significant differences between treatment groups or disease location cohorts in rates of CD-related hospitalizations.

Overall, these outcomes indicate no significant differences in cumulative rates of clinical response, clinical remission, mucosal healing, or treatment persistence with first-line vedolizumab or ustekinumab regardless of baseline disease location.

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Super-Responders in Patients With Moderate-to-Severe Crohn's Disease Treated With Subcutaneous Infliximab Maintenance Therapy: A Post Hoc Analysis of the LIBERTY-CD Study

An SC formulation of infliximab is available for the maintenance treatment of moderate-to-severe ulcerative colitis (UC) or moderate-to-severe CD following an IV infliximab product.[1] The approval was based on results of the randomized, phase 3 LIBERTY-CD trial, which demonstrated the superiority of SC infliximab over placebo as maintenance therapy after IV infliximab induction in patients with CD.[2]

At DDW 2024, a post hoc analysis from LIBERTY-CD was presented that grouped patients into response trajectories based on level of responses to SC infliximab therapy.[3] The analysis included 231 patients from the SC infliximab arm of LIBERTY-CD. Group-based trajectory modeling was used to develop response trajectories based on longitudinal patient-reported outcomes of abdominal pain and stool frequency.

Four categories of response trajectory were identified based on response rates, level of response, and outcomes. Super-responders (n=61) had a rapid and sustained improvement, fast responders (n=56) had a slightly lesser improvement that was sustained, slow responders (n=63) showed a gradual and sustained improvement, and limited responders (n=51) had a partial

ABSTRACT SUMMARY Ustekinumab as Monotherapy or in Combination With Thiopurines in the Treatment of Crohn's Disease and Ulcerative Colitis: Emulation of Two Target Trials Within the French Healthcare Databases

A retrospective French administrative database analysis was presented reviewing the effectiveness of ustekinumab with or without thiopurines in patients with CD and UC (Abstract Tu1815). Combination therapy with ustekinumab plus thiopurines was administered to approximately 10% of patients, including 11.6% of patients with CD (1315 of 11,343) and 10.3% of patients with UC (260 of 2529). There was no difference between combination therapy and monotherapy in the primary outcome, a composite endpoint of treatment failure defined by disease-related hospitalization, switch to another advanced therapy, or corticosteroid exposure at week 26. The week 26 treatment failure rates were 22.8% with combination therapy and 23.6% with monotherapy in patients with CD and 21.7% and 22.5%, respectively, in patients with UC. Hospitalizations and serious infections were also not significantly different between combination therapy and monotherapy. Researchers concluded that the findings support the use of ustekinumab monotherapy in patients with CD and UC.

Table. Week 54 Clinical Outcomes by Response Trajectory in Patients With Moderate-to-Severe Crohn's Disease Treated With Subcutaneous Infliximab Maintenance Therapy: A Post Hoc Analysis of the LIBERTY-CD Study

Response trajectory, n/N (%)	Outcome at week 54				
	Clinical remission[a]	Endoscopic response[b]	Corticosteroid-free remission[c]	Endoscopic remission[d]	Comprehensive disease control[e]
Super-Responders	45/61 (73.8)	39/61 (63.9)	14/22 (63.6)	26/61 (42.6)	23/61 (37.7)
Fast Responders	30/56 (53.6)	21/56 (37.5)	9/27 (33.3)	14/56 (25.0)	14/56 (25.0)
Slow Responders	46/63 (73.0)	37/63 (58.7)	12/23 (52.2)	26/63 (41.3)	21/63 (33.3)
Limited Responders	23/51 (45.1)	21/51 (41.2)	5/27 (18.5)	14/51 (27.5)	6/51 (11.8)
***P* value[f]**	.002048	.008708	.006773	.093548	.013364

[a]Clinical remission, an absolute CDAI score <150; [b]Endoscopic response, 50% decrease in SES-CD from baseline; [c]Corticosteroid-free remission at week 54, as being in clinical remission in addition to not receiving corticosteroids for ≥8 weeks prior to week 54, among patients who used oral corticosteroids at baseline; [d]Endoscopic remission, SES-CD of ≤4 and at least 2-point reduction from the baseline value with no segment sub-score of >1; [e]Comprehensive disease control was defined as achieving clinical remission, endoscopic response, fecal calprotectin normalization (fecal calprotectin ≤250 µg/g) and remission by health-related quality of life (SIBDQ score ≥50); [f]Within-column statistical comparisons were analyzed by Chi-square test.

CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for CD; SIBDQ, Short Inflammatory Bowel Disease Score.

Adapted from Schreiber et al. Abstract Su1767. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

improvement in the maintenance phase. These distinct response trajectories were evident and stabilized around weeks 10 to 14.

Compared with other subgroups, patients in the super-responder subgroup tended to have a lower baseline body weight, lower body mass index, and a higher CDAI score. In a multivariate analysis, factors significantly associated with the super-responder subgroup included baseline body mass index (odds ratio [OR], 0.91; *P*=.020) and week 10 infliximab serum level of at least 14 µg/mL (OR, 2.78; *P*=.003). However, researchers noted that there are limitations to predicting super-response status.

There was a trend toward higher predose infliximab serum levels in super-responders versus other response trajectories throughout the maintenance phase starting at week 10, with the difference reaching statistical significance at week 30.

Clinical outcomes at week 54 were most favorable in super-responders than in the other trajectories (Table). Clinical remission rates (CDAI <150) were 73.8% in super-responders, 53.6% in fast responders, 73.0% in slow responders, and 45.1% in limited responders (*P*=.002048). Endoscopic response rates (50% decrease in SES-CD) were 63.9%, 37.5%, 58.7%, and 41.2%, respectively (*P*=.008708). Corticosteroid-free remission rates were 63.6%, 33.3%, 52.2%, and 18.5%, respectively (*P*=.006773), and endoscopic remission rates were 42.6%, 25.0%, 41.3%, and 27.5%, respectively (*P*=.093548).

Safety profiles with SC infliximab were similar across response trajectory groups, as were rates of treatment-emergent SAEs and injection site reactions.

Researchers concluded that additional studies evaluating the association between super-response status and long-term outcomes are needed.

A new, convenient, subcutaneous modality of delivery for infliximab has been approved in the United States. Understanding which patients respond best to this delivery mechanism is important. Post hoc data show an association between BMI and rapid, durable remission with the subcutaneous delivery. In my practice, I will likely consider individual patient factors like BMI when recommending a maintenance strategy. —Millie D. Long, MD, MPH

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2. Colombel JF, Hanauer SB, Sandborn W, et al. Subcutaneous infliximab (CT-P13 SC) as maintenance therapy for Crohn's disease: a phase 3, randomised, placebo-controlled study (LIBERTY-CD). Abstract DOP86. Presented at: ECCO 2023; March 1-3, 2023; Copenhagen, Denmark.
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Risankizumab Effectiveness in Ustekinumab-Naive and Ustekinumab-Experienced Patients With Crohn's Disease: Real-World Data From a Large Tertiary Center

The efficacy of risankizumab in patients with prior failure of ustekinumab has not been well described. Thus, a real-world analysis was undertaken to evaluate the effectiveness of risankizumab based on prior treatment with ustekinumab.[1] This prospective, observational study included 143 patients with active CD, defined as a Harvey-Bradshaw Index (HBI) of 5 or greater, FCP greater than 250 µg/g, or evidence of active disease per ileocolonoscopy or imaging. Patients with ostomy, J-pouch, or surgery within 6 months of starting treatment were excluded.

Researchers prospectively monitored HBI at weeks 2, 4, 8, 12, 26, and 52, and monitored FCP at weeks 12, 26, and 52. Key outcomes included clinical remission, defined as a modified HBI less than 5, steroid-free clinical remission, treatment persistence, and change in FCP over time.

The cohort included 67 ustekinumab-naive patients and 76 ustekinumab-experienced patients. Ustekinumab-experienced patients were older than ustekinumab-naive patients (median age, 45 vs 36 years), were more likely to have received at least 2 advanced therapies (92.1% vs 32.8%), and were more likely to have undergone bowel resection (68% vs 47.7%).

Clinical remission rates were numerically higher among ustekinumab-naive patients compared with ustekinumab-experienced patients throughout the follow-up period, but this trend reached statistical significance for steroid-free clinical remission only at week 12 (74% vs 54%; *P*=.03) (Figure 4). At week 52, rates of clinical remission in the ustekinumab-naive and ustekinumab-experienced patients were 66% and

ABSTRACT SUMMARY Real-World Effectiveness and Safety of Upadacitinib in Crohn's Disease: A Multi-Centre Study

Another retrospective real-world analysis reported on the effectiveness and safety of upadacitinib in patients with CD (Abstract Tu1882). The analysis included 227 patients initiating upadacitinib at one of the 8 REBOOT-IBD consortium centers. The primary endpoint, clinical remission at 12 weeks, was achieved in 48.6% overall, 44.9% of tofacitinib-exposed patients, 49.1% of tofacitinib-naive patients. Endoscopic remission rates were 37.2% overall, 42.9% in tofacitinib-exposed patients, and 36.1% in tofacitinib-naive patients. Prior exposure to tofacitinib and total number of prior biologics did not affect treatment outcomes. Factors significantly associated with a lower likelihood of attaining clinical remission included duration of disease (OR, 0.95; *P*=.0021), stricturing behavior (OR, 0.28; *P*=.0006), and penetrating behavior (OR, 0.43; *P*=.03). Nonsmokers were more likely than smokers to attain clinical response (OR, 0.27; *P*=.04). No factors were significantly associated with endoscopic remission.

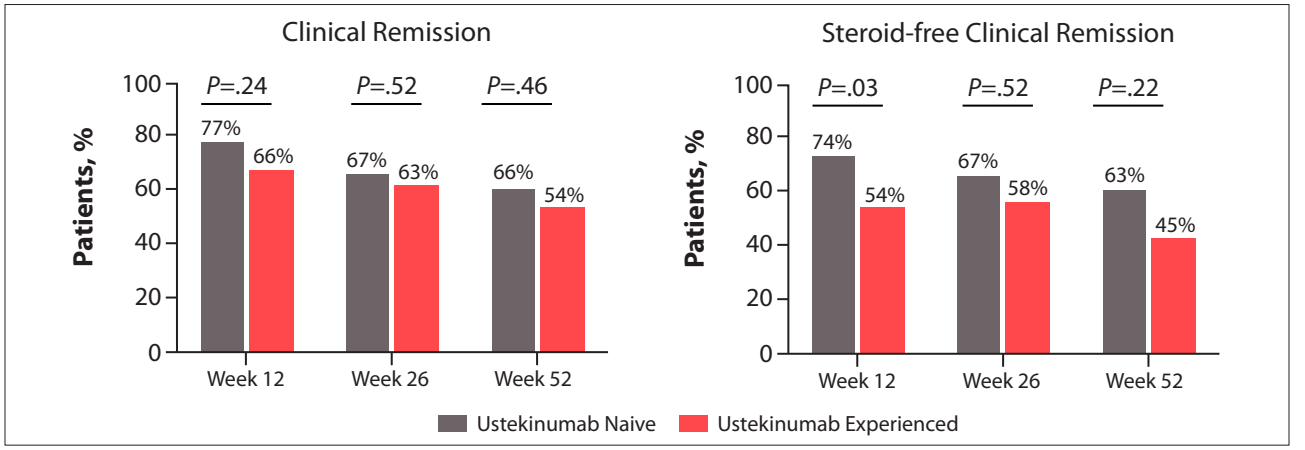


Figure 4. Risankizumab effectiveness in ustekinumab-naive and ustekinumab-experienced patients with Crohn's disease: real-world data from a large tertiary center. Adapted from Zinger et al. Oral Presentation 1177. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

54%, respectively (*P*=.46), and rates of steroid-free clinical remission were 63% and 45%, respectively (*P*=.22).

In a multivariate analysis, no factors were significantly associated with likelihood of steroid-free clinical remission at 1 year, including prior ustekinumab exposure, lack of response to prior ustekinumab, disease duration, history of bowel resection, number of previous therapies for advanced disease, and HBI at baseline.

No significant differences were observed between the ustekinumab-naive and ustekinumab-experienced patients in regard to the proportion of patients remaining on risankizumab to week 52 (69% vs 80%; *P*=.30) and the proportion of steroid-free clinical remissions that were maintained from week 12 through week 52 (76% vs 75%; *P*>.99).

FCP levels declined to a similar extent in both ustekinumab-naive and ustekinumab-experienced patients, with at least 80% of evaluable patients in each group attaining FCP less than 250 µg/g by week 52.

Researchers concluded that clinical responses to risankizumab were generally comparable regardless of ustekinumab exposure but appeared to be less robust in ustekinumab-experienced patients. They suggested that the nonsignificant differences noted between arms could indicate that ustekinumab-experienced patients are a more difficult-to-treat population and could reflect a higher HBI at baseline in those patients. They added that these findings support risankizumab as an option for patients with CD regardless of prior ustekinumab exposure.

Real-world data often guide therapy selection in scenarios with limited data from clinical trials. This real-world study demonstrates that an IL-23 inhibitor can be utilized in patients with CD regardless of prior exposure to an IL-12/IL-23 inhibitor.
—Millie D. Long, MD, MPH

Reference

1. Zinger A, Choi D, Choi NK, et al. Risankizumab effectiveness in ustekinumab-naive and ustekinumab-experienced patients with Crohn's disease: real-world data from a large tertiary center. Abstract 1177. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

Improvement in Inflammatory Bowel Disease Questionnaire Items: Fatigue, Depression, Anxiety, and Bowel Urgency in Patients With Crohn's Disease Treated With Upadacitinib in Phase 3 Trials

Another presentation at DDW 2024 on upadacitinib in CD focused on specific HRQOL outcomes as measured by the IBDQ.[1] HRQOL outcomes in clinical trials of CD therapies are important, as CD is associated with substantial mental and physical effects that negatively affect HRQOL. After adjusting for other factors, individuals with IBD report a higher incidence of psychiatric disorders.[2] The relapsing and remitting disease course, uncomfortable symptoms, and side effects of treatment also negatively affect QOL.[3]

As reported in the U-EXCEL, U-EXCEED, and U-ENDURE trials, upadacitinib is associated with improvements in HRQOL over placebo as assessed by the IBDQ, which is a well-validated measure of HRQOL in patients with IBD.[4] To better understand changes in HRQOL associated with upadacitinib treatment, an

ABSTRACT SUMMARY Upadacitinib Is Effective and Safe for the Treatment of Ulcerative Colitis and Crohn's Disease: 1-Year Prospective Real-World Experience

A prospective real-world study was presented that reviewed the experience using the novel selective Janus kinase 1 inhibitor upadacitinib in 110 patients with moderate-to-severe UC and CD, 28% who were tofacitinib-exposed (Abstract Mo1848). Efficacy was assessed using the Simple Clinical Colitis Activity Index, HBI, CRP, and FCP. After 1 year, 54 patients remained on therapy; of the 56 patients who discontinued therapy, 13 discontinued owing to AEs. The most common AEs leading to discontinuation were dermatologic, occurring in 4 patients; there was 1 case of shingles leading to discontinuation. In patients with UC, week 52 clinical response and clinical remission rates were 56.7% (17/30) and 96.7% (29/30), respectively. In patients with CD, week 52 clinical response and clinical remission rates were 58.8% (10/17) and 76.5% (13/17), respectively. No serious infections or SAEs were reported.

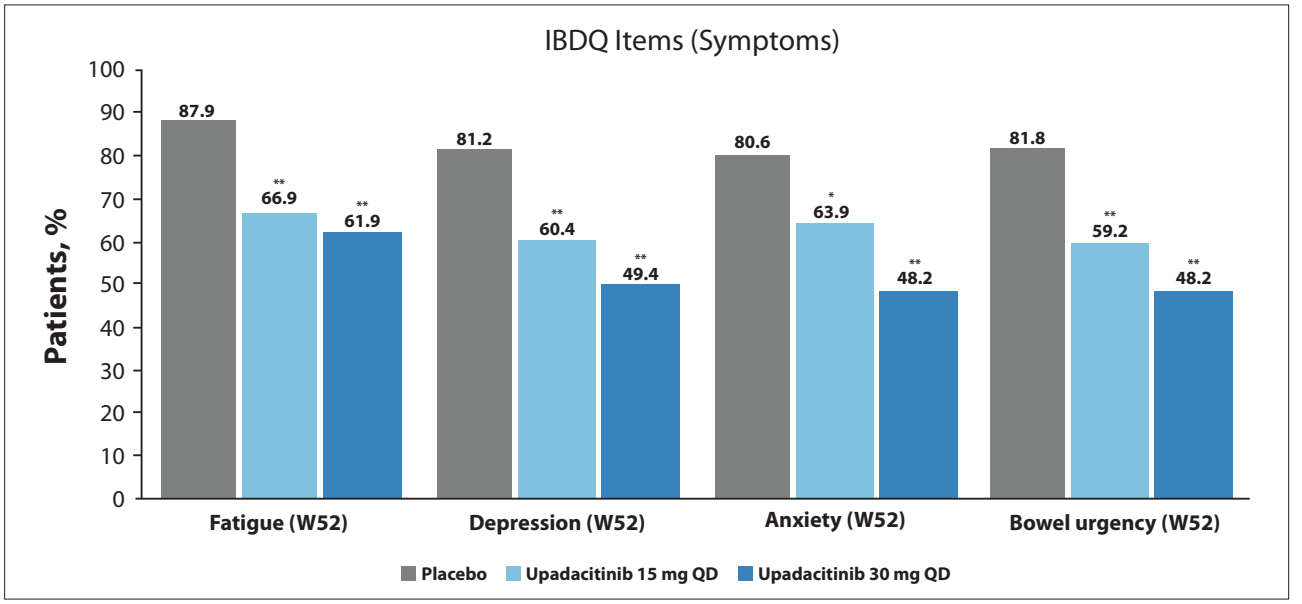


Figure 5. Patients with Crohn's disease treated with upadacitinib in phase 3 trials who reported IBDQ symptoms "all/most/a good bit/some of the time" for the fatigue, depression, anxiety, and bowel urgency items at the end of the maintenance period. IBDQ, Inflammatory Bowel Disease Questionnaire; QD, once daily; W52, week 52. *P<.001 for upadacitinib 15 mg QD vs placebo or upadacitinib 30 mg QD vs placebo. **P<.0001 for upadacitinib 15 mg QD vs placebo or upadacitinib 30 mg QD vs placebo. Adapted from Loftus Jr. et al. Abstract Su1863. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.

analysis was conducted to investigate changes in specific IBDQ items in patients enrolled across the U-EXCEL, U-EXCEED, and U-ENDURE trials.[1]

The tool includes 32 items, with each assessed on a 7-point scale ranging from 7 (the symptom occurs none of the time) to 1 (the symptom occurs all of the time). The current analysis focused on fatigue, depression, anxiety, and bowel urgency to elucidate how IBD symptoms and severity change with treatment.

In the phase 3 upadacitinib trials, IBDQ outcomes were assessed at baseline, week 4, week 12, and week 52. This analysis grouped responses for each item into 2 categories: one for patients reporting the symptom "all," "most," "a good bit," or "some" of the time, and the other for patients reporting the symptom "a little," "hardly," or "none" of the time.

During the induction treatment period, the proportion of patients reporting having symptoms "all" to "some" of the time was significantly lower in week 12 in the upadacitinib arm than in the placebo arm for fatigue (52.1% vs 78.4%; P<.0001), depression (35.5% vs 53.9%; P<.0001), anxiety (37.2% vs 59.6%; P<.0001), and bowel urgency (31.9% vs 55.6%; P<.0001).

These trends were sustained through the 52-week maintenance phase, with significant reductions in fatigue, depression, anxiety, and bowel urgency reported with either upadacitinib maintenance dose (15 mg or 30 mg once daily) versus placebo (Figure 5).

Early improvements in fatigue, depression, anxiety, and bowel urgency are seen with upadacitinib in patients with CD. Janus kinase inhibitors are known for rapid improvements in IBD-related symptoms, but now we have data on similar rapidity with respect to improvements in quality of life.
—Millie D. Long, MD, MPH

References

1. Loftus Jr. EV, Rubin DT, Louis E, et al. Improvement in inflammatory bowel disease questionnaire items: fatigue, depression, anxiety, and bowel urgency in patients with Crohn's disease treated with upadacitinib in phase 3 trials. Abstract Su1863. Presented at: DDW 2024; May 18-21, 2024; Washington, DC.
2. Bernstein CN, Hitchon CA, Walld R, et al. Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(2):360-368.
3. Mitropoulou MA, Fradelos EC, Lee KY, et al. Quality of life in patients with inflammatory bowel disease: importance of psychological symptoms. *Cureus*. 2022;14(8):e28502.
4. Chen XL, Zhong LH, Wen Y, et al. Inflammatory bowel disease-specific health-related quality of life instruments: a systematic review of measurement properties. *Health Qual Life Outcomes*. 2017;15(1):177.

THE DATA IS IN

See Results From A Head-to-Head Trial

Skyrizi®
risankizumab-rzaa

For adults with moderately to severely active Crohn's disease[1]

SKYRIZI PROVIDES THE OPPORTUNITY FOR ENDOSCOPIC AND SYMPTOM CONTROL. **FOR YOUR PATIENTS, THAT'S EVERYTHING.**

ENDOSCOPIC AND SYMPTOM CONTROL ACROSS PIVOTAL TRIAL CO-PRIMARY ENDPOINTS[1]

	ADVANCE Mixed Population*	MOTIVATE Biologic Failure Population†	FORTIFY Mixed Population*
CO-PRIMARY ENDPOINT: Endoscopic Response (SES-CD)	SKYRIZI 40%, PLACEBO 12%	SKYRIZI 29%, PLACEBO 11%	SKYRIZI 360 mg 48%, SKYRIZI 180 mg 50%, PBO (Induction Responders) 22% $p<0.05$; all p-values are SKYRIZI treatment arms vs placebo.
CO-PRIMARY ENDPOINT: Clinical Remission (CDAI)	SKYRIZI 45%, PLACEBO 25%	SKYRIZI 42%, PLACEBO 20%	SKYRIZI 360 mg 57%, SKYRIZI 180 mg 61%, PBO (Induction Responders) 46% $p<0.05$; all p-values are SKYRIZI treatment arms vs placebo.
SECONDARY ENDPOINT: Endoscopic Remission	SKYRIZI 24%, PLACEBO 9%	SKYRIZI 19%, PLACEBO 4%	SKYRIZI 360 mg 41%, SKYRIZI 180 mg 33%, PBO (Induction Responders) 13% **This endpoint was not statistically significant under the prespecified multiple testing procedure.**
	SKYRIZI 600 mg IV n=336, PLACEBO n=175 $p<0.001$	SKYRIZI 600 mg IV n=191, PLACEBO n=187 $p<0.001$	SKYRIZI 360 mg SC n=117, SKYRIZI 180 mg SC n=135, PLACEBO (Induction Responders) n=130

Placebo (Induction Responders): Patients who achieved CDAI clinical response (CR-100) to SKYRIZI induction therapy and were randomized to receive placebo in the maintenance study.

Clinical Remission: Defined as a CDAI score <150 points.[1]

Endoscopic Remission: SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, as scored by a central reviewer.

Endoscopic Response: Defined as a decrease in SES-CD >50% from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease, based on central reading. The sections evaluated on endoscopy are the rectum, sigmoid and left colon, transverse colon, right colon and ileum (per SES-CD assessment).

PIVOTAL TRIAL STUDY DESIGNS

ADVANCE (N=850) and **MOTIVATE** (N=569) Induction studies were 12-week, randomized, double-blind, placebo-controlled studies that evaluated the efficacy and safety of SKYRIZI in patients with moderately to severely active Crohn's disease who demonstrated prior treatment failure to conventional and/or biologic treatment.[2] Patients received an IV infusion of SKYRIZI 600 mg, 1200 mg, or placebo at Weeks 0, 4, and 8.[1]

FORTIFY (N=382) Maintenance study was a 52-week study that evaluated the efficacy and safety of SKYRIZI in patients who achieved clinical response (decrease in CDAI ≥100) from SKYRIZI induction in the ADVANCE and MOTIVATE studies. Patients were randomized to SKYRIZI 180 mg SC, SKYRIZI 360 mg SC, or placebo at Week 12 and every 8 weeks thereafter.[1]

INDICATION AND IMPORTANT SAFETY INFORMATION FOR SKYRIZI[1]

INDICATION[1]

SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

IMPORTANT SAFETY INFORMATION[1]

Hypersensitivity Reactions
SKYRIZI® (risankizumab-rzaa) is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately.

Infection
SKYRIZI may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

Tuberculosis (TB)
Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Hepatotoxicity in Treatment of Crohn's Disease
Drug-induced liver injury was reported in a patient with Crohn's disease who was hospitalized for a rash during induction dosing of SKYRIZI. For the treatment of Crohn's disease, evaluate liver enzymes and bilirubin at baseline and during induction (12 weeks); monitor thereafter according to routine patient management. Consider an alternate treatment for patients with evidence of liver cirrhosis. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct your patient to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Administration of Vaccines
Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating SKYRIZI, complete all age appropriate vaccinations according to current immunization guidelines.

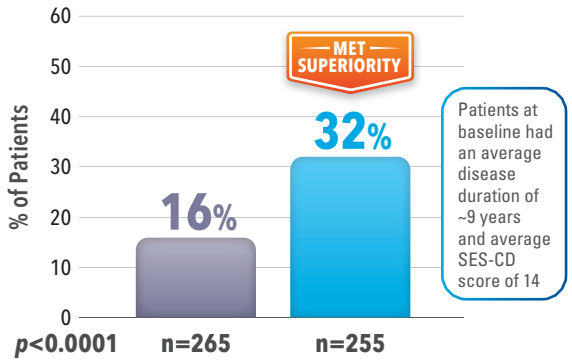
SEQUENCE HEAD-TO-HEAD PRIMARY ENDPOINTS DATA[3,4]

STUDY DESIGN

SEQUENCE was a Phase 3, multicenter, randomized, open-label, efficacy assessment-blinded[‡] study of SKYRIZI (n=255) compared to STELARA® (ustekinumab)[§] (n=265) for the treatment of adult patients with moderate to severe Crohn's disease who have failed anti-TNF therapy. Eligible patients were randomized (1:1) to receive either SKYRIZI (600 mg IV to 360 mg SC) or STELARA® (ustekinumab) (weight-based[‖] IV to 90 mg SC). After induction dosing was completed, patients remained on their respective therapy throughout the duration of the maintenance period (treat-through study design). Dosing for both treatment arms was aligned to the US Prescribing Information with no dose escalation allowed throughout the trial.

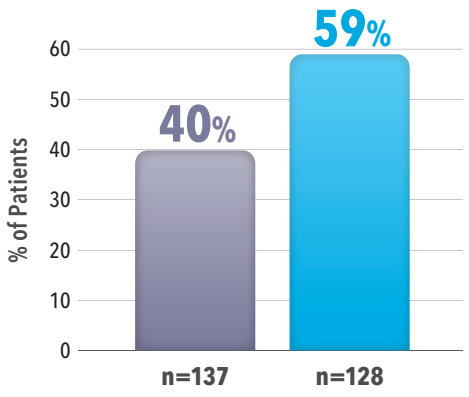
POWERFUL SUPERIORITY DATA[3,4]

Endoscopic Remission at Week 48 (Superiority Endpoint, NRI-MI)



DEMONSTRATED SYMPTOM RELIEF DATA[3,4]

Clinical Remission at Week 24 (Non-inferiority Endpoint, NRI-MI)



STELARA® (ustekinumab)[§] (90 mg SC Q8W) SKYRIZI (360 mg SC Q8W)

[‡]The investigator and site personnel were blinded to the results of the clinical outcomes (CDAI) for the duration of the study, and endoscopies were centrally read with assessors blinded to study drug.

[§]**Active Comparator:** 31 patients received US-approved ustekinumab. All other patients received European Union-approved ustekinumab. The comparability between US- and non-US-approved ustekinumab has not been established.

Superiority Endpoint: This primary endpoint was evaluated based on a 0.05, 2-sided significance level.

Endoscopic Remission: SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, as scored by a central reviewer.

Non-inferiority Endpoint: This primary endpoint was measured in ~50% of total population. This measure was based on a non-inferiority margin of 10% at the 0.05, 2-sided significance level, where a margin of 10% was selected based on physicians' perspective on the clinical meaningfulness of inflammatory bowel disease trial results: an International Organization for the Study of Inflammatory Bowel Disease (IOIBD) survey.[5]

Clinical Remission: Defined as a CDAI score <150 points.[1]

NRI-MI: Non-responder imputation for missing data with the exception that if the reason for missing data is due to COVID-19 infection or logistical restriction due to pandemic or geopolitical conflict, the patient's assessment will be imputed using multiple imputation.

INTERESTED IN SEEING ADDITIONAL RESULTS?
WWW.SKYRIZIHCP.COM

Adverse Reactions

Most common (>3%) adverse reactions associated with SKYRIZI in Crohn's disease are upper respiratory infections, headache, and arthralgia in induction and arthralgia, abdominal pain, injection site reactions, anemia, pyrexia, back pain, arthropathy, and urinary tract infection in maintenance.

Lipid Elevations: Increases from baseline and increases relative to placebo were observed at Week 4 and remained stable to Week 12 in patients treated with SKYRIZI in Crohn's disease.

Dosage Forms and Strengths: SKYRIZI is available in a 600 mg/10 mL single-dose vial for intravenous infusion and a 180 mg/1.2 mL or 360 mg/2.4 mL single-dose prefilled cartridge with on-body injector.

Please see the brief summary of the full Prescribing Information on the following pages.

CDAI=Crohn's disease activity index; IV=intravenous; SC=subcutaneous; SES-CD=simple endoscopic score for Crohn's disease; TNF=tumor necrosis factor.

* The mixed population includes patients who had inadequate response, loss of response, or intolerance to one or more biologics (biologic failure), as well as patients who had never demonstrated inadequate response, loss of response, or intolerance to a biologic (bio-naïve; includes 13% in ADVANCE and 8% in FORTIFY who were bio-exposed).

[†] Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologics.

[‖] Baseline STELARA® (ustekinumab) IV dose is weight-based: ≤55 kg: 260 mg dose, >55 kg to 85 kg: 390 mg dose, or >85 kg: 520 mg dose.

STELARA® is a registered trademark of Johnson & Johnson. See US Prescribing Information for further information.

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet.* 2022; 399(10340):2015-2030. **3.** Peyrin-Biroulet L, Chapman JC, Colombel J-F, et al. Risankizumab versus ustekinumab for patients with moderate to severe Crohn's disease: results from the Phase 3b SEQUENCE study. Presented at United European Gastroenterology Week (UEGW 2023), October 14 – 17, 2023, Copenhagen, Denmark. **4.** Data on File, AbbVie Inc, ABVRRTI76928. **5.** Olivera P, Sandborn WJ, Panés J, et al. Physicians' perspective on the clinical meaningfulness of inflammatory bowel disease trial results: an International Organization for the Study of Inflammatory Bowel Disease (IOIBD) survey. *Aliment Pharmacol Ther.* 2018;47(6):773-783.

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SKYRIZI® (sky-RIZZ-ee) (risankizumab-rzaa) injection, for subcutaneous or intravenous use

90 mg/mL single-dose prefilled syringe
150 mg/mL single-dose pen and prefilled syringe
600 mg/10 mL single-dose vial for intravenous infusion
180 mg/1.2 mL single-dose prefilled cartridge with on-body injector
360 mg/2.4 mL single-dose prefilled cartridge with on-body injector

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Plaque Psoriasis

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriatic Arthritis

SKYRIZI is indicated for the treatment of active psoriatic arthritis in adults.

Crohn's Disease

SKYRIZI is indicated for the treatment of moderately to severely active Crohn's disease in adults.

CONTRAINDICATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately *[see Adverse Reactions]*.

Infections

SKYRIZI may increase the risk of infections *[see Adverse Reactions]*.

Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the PsO-3 study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

Hepatotoxicity in Treatment of Crohn's Disease

A serious adverse reaction of drug-induced liver injury in conjunction with a rash that required hospitalization was reported in a patient with Crohn's disease (ALT 54x ULN, AST 30x ULN, and total bilirubin 2.2x ULN) following two 600 mg intravenous doses of SKYRIZI. The liver test abnormalities resolved following administration of steroids. SKYRIZI was subsequently discontinued.

For the treatment of Crohn's disease, evaluate liver enzymes and bilirubin at baseline, and during induction at least up to 12 weeks of treatment. Monitor thereafter according to routine patient management.

Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Tuberculosis *[see Warnings and Precautions]*
- Hepatotoxicity in Treatment of Crohn's Disease *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse drug reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plaque Psoriasis

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared with 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In Studies PsO-1 and PsO-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

Psoriatic Arthritis

The overall safety profile observed in subjects with psoriatic arthritis treated with SKYRIZI is generally consistent with the safety profile in subjects with plaque psoriasis. Additionally, in the Phase 3 placebo-controlled trials the incidence of hepatic events was higher in the SKYRIZI group (5.4%, 16.7 events per 100 patient years) compared to the placebo group (3.9%, 12.6 events per 100 patient years). Of these, the most common events that were reported more frequently in both the placebo group and the SKYRIZI group were ALT increased (placebo: n=12 (1.7%); SKYRIZI: n=16 (2.3%)), AST increased (placebo: n=9 (1.3%); SKYRIZI: n=13 (1.8%)), and GGT increased (placebo: n=5 (0.7%); SKYRIZI: n=8 (1.1%)). There were no serious hepatic events reported. The incidence of hypersensitivity reactions was higher in the SKYRIZI group (n=16, 2.3%) compared to the placebo group (n=9, 1.3%). In the Phase 3 placebo-controlled trials, hypersensitivity reactions reported at a higher rate in the SKYRIZI group included rash (placebo: n=4 (0.6%); SKYRIZI: n=5 (0.7%), allergic rhinitis (placebo: n=1 (0.1%); SKYRIZI: n=2 (0.3%), and facial swelling (placebo: n=0 (0.0%); SKYRIZI n=1 (0.1%). One case of anaphylaxis was reported in a subject who received SKYRIZI in the Phase 2 clinical trial.

Crohn's Disease

SKYRIZI was studied up to 12 weeks in subjects with moderately to severely active Crohn's disease in two randomized, double-blind, placebo-controlled induction studies (CD-1, CD-2) and a randomized, double-blind, placebo-controlled, dose-finding study (CD-4; NCT02031276). Long-term safety up to 52 weeks was evaluated in subjects who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (CD-3).

In the two induction studies (CD-1, CD-2) and the dose finding study (CD-4), 620 subjects received the SKYRIZI intravenous induction regimen at Weeks 0, 4 and 8. In the maintenance study (CD-3), 297 subjects who achieved clinical response, defined as a reduction in CDAI of at least 100 points from baseline after 12 weeks of induction treatment with intravenous SKYRIZI in studies CD-1 and CD-2, received a maintenance regimen of SKYRIZI either 180 mg or 360 mg subcutaneously at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks.

Adverse reactions reported in > 3% of subjects in induction studies and at a higher rate than placebo are shown in Table 2.

Table 2. Adverse Drug Reactions Reported in > 3% of Subjects with Crohn's Disease Treated with SKYRIZI in Placebo-Controlled 12-Week Induction Studies

Adverse Drug Reactions	SKYRIZI 600 mg Intravenous Infusion[a] N = 620 n (%)	Placebo N = 432 n (%)
Upper respiratory infections[b]	66 (10.6)	40 (9.3)
Headache[c]	41 (6.6)	24 (5.6)
Arthralgia	31 (5.0)	19 (4.4)

[a] SKYRIZI 600 mg as an intravenous infusion at Week 0, Week 4, and Week 8.
[b] Includes: influenza like illness, nasopharyngitis, influenza, pharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, COVID-19, nasal congestion, respiratory tract infection viral, viral pharyngitis, tonsillitis, upper respiratory tract inflammation
[c] Includes: headache, tension headache

Adverse reactions reported in >3% of subjects in the maintenance study and at a higher rate than placebo are shown in Table 3.

Table 3. Adverse Reactions Reported in >3% of Subjects with Crohn's Disease Treated with SKYRIZI[a] in Placebo-Controlled 52-Week Maintenance Study (CD-3)

Adverse Drug Reactions	SKYRIZI 180 mg Subcutaneous Injection N = 155 n (%)	SKYRIZI 360 mg Subcutaneous Injection N = 142 n (%)	Placebo N = 143 n (%)
Arthralgia	13 (8.4)	13 (9.2)	12 (8.4)
Abdominal pain[b]	9 (5.8)	12 (8.5)	6 (4.2)
Injection site reactions[c,d]	7 (4.5)	8 (5.6)	4 (2.8)
Anemia	7 (4.5)	7 (4.9)	6 (4.2)
Pyrexia	4 (2.6)	7 (4.9)	4 (2.8)
Back pain	3 (1.9)	6 (4.2)	3 (2.1)
Arthropathy	1 (0.6)	5 (3.5)	2 (1.4)
Urinary tract infection	1 (0.6)	5 (3.5)	4 (2.8)

[a] SKYRIZI 180 mg or 360 mg at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks
[b] Includes: abdominal pain, abdominal pain upper, abdominal pain lower
[c] Includes: injection site rash, injection site erythema, injection site swelling, injection site urticaria, injection site warmth, injection site pain, injection site hypersensitivity, injection site reaction
[d] Some subjects had multiple occurrences of injection site reactions. In this table, injection site reactions are counted only once per subject for the rate calculations.

Specific Adverse Drug Reactions

Infections

In the maintenance study (CD-3) through Week 52, the rate of infections was 32.3% (50.2 events per 100 subject-years) in subjects who received SKYRIZI 180 mg and 36.6% (60.8 events per 100 subject-years) in subjects who received SKYRIZI 360 mg compared to 36.4% (60.3 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction. The rate of serious infections was 2.6% (2.7 events per 100 subject-years) in subjects who received SKYRIZI 180 mg and 5.6% (7.4 events per 100 subject-years) in subjects who received SKYRIZI 360 mg compared to 2.1% (2.4 events per 100 subject-years) in subjects who received placebo after SKYRIZI induction.

Lipid Elevations

Elevations in lipid parameters (total cholesterol and low-density lipoprotein cholesterol [LDL-C]) were first assessed at 4 weeks following initiation of SKYRIZI in the induction trials (CD-1, CD-2). Increases from baseline and increases relative to placebo were observed at Week 4 and remained stable to Week 12. Following SKYRIZI induction, mean total cholesterol increased by 9.4 mg/dL from baseline to a mean absolute value of 175.1 mg/dL at Week 12. Similarly, mean LDL-C increased by 6.6 mg/dL from baseline to a mean absolute value of 92.6 mg/dL at Week 12. Mean LDL-C increased by 3.1 mg/dL from baseline to a mean absolute value of 99.0 mg/dL at Week 52 with SKYRIZI 180 mg maintenance treatment and by 2.3 mg/dL from baseline to a mean absolute value of 102.2 mg/dL at Week 52 with SKYRIZI 360 mg maintenance treatment.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

Plaque Psoriasis

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

Psoriatic Arthritis

By Week 28, approximately 12.1% (79/652) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing. Antibodies to risankizumab-rzaa were not associated with changes in clinical response for psoriatic arthritis. A higher proportion of subjects with anti-drug antibodies experienced hypersensitivity reactions (6.3% (5/79)) and injection site reactions (2.5% (2/79)) compared to subjects without anti-drug antibodies (3.8% (22/574) with hypersensitivity reactions and 0.7% (4/574) with injection site reactions). None of these hypersensitivity and injection site reactions led to discontinuation of risankizumab-rzaa.

Crohn's Disease

By Week 64, antibodies to risankizumab-rzaa developed in approximately 3.4% (2/58) of subjects treated with SKYRIZI induction followed by 360 mg maintenance regimen. No subjects (0/57) treated with SKYRIZI induction followed by 180 mg maintenance regimen developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had antibodies that were classified as neutralizing.

Postmarketing Experience

The following adverse reactions have been reported during post-approval of SKYRIZI. 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 SKYRIZI exposure:

- *Skin and subcutaneous tissue disorders*: eczema and rash

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161 or visiting http://glowpregnancyregistry.com.

Risk Summary

Available pharmacovigilance and clinical trial data with risankizumab use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Although there are no data on risankizumab-rzaa, monoclonal antibodies can be actively transported across the placenta, and SKYRIZI may cause immunosuppression in the in utero-exposed infant**.** There are adverse pregnancy outcomes in women with inflammatory bowel disease *(see Clinical Considerations).*

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 or 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. Increased fetal/infant loss was noted in pregnant monkeys at the 50 mg/kg dose *(see Data).* The 50 mg/kg dose in pregnant monkeys resulted in approximately 10 times the exposure (AUC) in humans administered the 600 mg induction regimen and 39 times the exposure (AUC) to the 360 mg maintenance doses, respectively. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal adverse reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because risankizumab may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to SKYRIZI in utero. There are insufficient data regarding infant serum levels of risankizumab at birth and the duration of persistence of risankizumab in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 5 months after birth should be considered because of the half-life of the product.

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition, and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology, or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared with the vehicle control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg and the NOAEL for developmental toxicity was identified as 5 mg/kg. On an exposure (AUC) basis, the 5 mg/kg dose in pregnant monkeys resulted in approximately 1.24 times the exposure in humans administered the 600 mg induction regimen and 5 times the exposure in humans administered the 360 mg maintenance doses, respectively. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17%-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to risankizumab-rzaa are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of SKYRIZI have not been established in pediatric patients.

Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in SKYRIZI exposure, safety, or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

Clinical studies of SKYRIZI for the treatment of Crohn's disease did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

No clinically meaningful differences in the pharmacokinetics of risankizumab-rzaa were observed in geriatric subjects compared to younger adult subjects with Crohn's disease.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypersensitivity Reactions

Advise patients to discontinue SKYRIZI and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions].*

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions].*

Hepatotoxicity in Treatment of Crohn's Disease

Inform patients that SKYRIZI may cause liver injury, especially during the initial 12 weeks of treatment. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of liver dysfunction. (e.g., unexplained rash, nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) *[see Warnings and Precautions].*

Administration of Vaccines

Advise patients that vaccination with live vaccines is not recommended during SKYRIZI treatment and immediately prior to or after SKYRIZI treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SKYRIZI prior to a potential vaccination *[see Warnings and Precautions].*

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique.

If using SKYRIZI 90 mg/mL, instruct patients or caregivers to administer two 90 mg single-dose syringes to achieve the full 180 mg maintenance dose or four 90 mg single-dose syringes to achieve the full 360 mg maintenance dose of SKYRIZI for Crohn's disease.

Instruct patients or caregivers in the technique of pen or syringe disposal.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to SKYRIZI during pregnancy *[see Use in Specific Populations].*

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