GASTROENTEROLOGY & HEPATOLOGY
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A SPECIAL MEETING REVIEW EDITION

Highlights in Crohn's Disease From Digestive Disease Week 2025

A Review of Selected Presentations From DDW 2025

May 3-6, 2025 • San Diego, California

Special Reporting on:

- One-Year Comparative Effectiveness and Safety of Upadacitinib Versus Risankizumab for CD
- Corticosteroid-Sparing Effects of Treatment With Guselkumab in Patients With Moderately to Severely Active CD: Phase 3 GRAVITI Study Results Through Week 48
- Comparative Effectiveness of Risankizumab Versus Ustekinumab in Bio-naive CD Patients: A Real-World Multicenter Retrospective Cohort Study
- Low Remission Recapture After Ustekinumab Dose Optimization in CD: Results of the Randomized Placebo-Controlled Double-Blind REScUE Study
- Dual-Targeted Therapy With Risankizumab and Upadacitinib Is Clinically and Biochemically Effective in Medically Complex CD
- Long-Term Efficacy and Safety of Mirikizumab Following 104 Weeks of Continuous Treatment for CD: Results From the VIVID-2 Open-Label Extension Study
- Impact of Immunogenicity on 2-Year Clinical Outcomes in Patients With Moderate-to-Severe CD Treated With Subcutaneous Infliximab: A Post Hoc Analysis of the Phase 3 LIBERTY-CD Study

PLUS Meeting Abstract Summaries

With Expert Comments by:

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RINVOQ®
upadacitinib

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

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

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

PUT CROHN'S IN CHECK AND KEEP IT THERE

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 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.

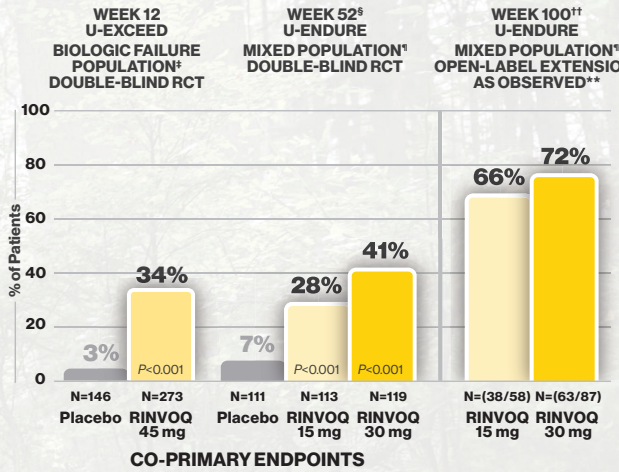
SAFETY CONSIDERATIONS[1]

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.

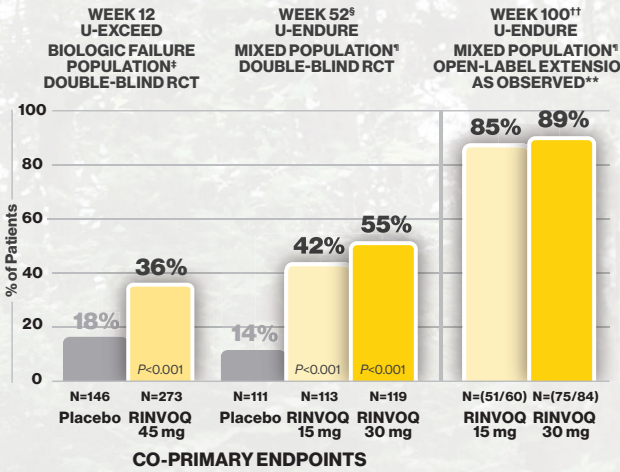
Mortality: A higher rate of all-cause mortality, including sudden cardiovascular (CV) death, was observed with a Janus kinase inhibitor (JAKi) in a study comparing another JAKi with tumor necrosis factor (TNF) blockers in rheumatoid arthritis (RA) patients ≥50 years with ≥1 CV risk factor.

~2 YEARS OF DATA

ENDOSCOPIC RESPONSE[1,4,5*]



CLINICAL REMISSION[1,4,5†]



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.

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. **5.** Data on File. ABVRRTI79272.

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 adult patients with rheumatoid arthritis were treated with RINVOQ 15 mg or upadacitinib 30 mg tablets once daily 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 tablets once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg tablets once daily and 251 patients received RINVOQ 30 mg tablets 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 tablets 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 tablets once daily and 229 patients received RINVOQ 30 mg tablets 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 it is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole, clarithromycin, and grapefruit), which may increase the risk of adverse reactions. Monitor patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondylarthritis, or pJIA closely for adverse reactions when co-administering RINVOQ 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 it is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect. 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 tablet dose, 0.8 and 7.6 times the 30 mg tablet 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 tablet dose, 0.9 times the 30 mg tablet 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 tablet dose, 0.15 times the 30 mg tablet 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 tablet dose, 7.6 times the 30 mg tablet 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 tablet dose, 1.1 times the 30 mg tablet 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 tablet dose, 1.4 times the 30 mg tablet 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

Ankylosing Spondylitis, Non-radiographic Axial Spondyloarthritis, Ulcerative Colitis, and Crohn's Disease

The safety and effectiveness of RINVOQ in pediatric patients with ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, or 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, non-radiographic axial spondyloarthritis, or pJIA 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 of RINVOQ 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 of RINVOQ 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 is therefore not recommended.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or pJIA 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 of RINVOQ 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 tablet dose, 2 and 5 times the 30 mg tablet 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 tablet dose, 11 and 43 times the 30 mg tablet 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 and caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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 RINVOQ *[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]*.

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One-Year Comparative Effectiveness and Safety of Upadacitinib Versus Risankizumab for CD

Two newer treatment options for patients with Crohn's disease (CD) are the selective Janus kinase 1 (JAK1) inhibitor upadacitinib and the interleukin-23 (IL-23) p19 monoclonal antibody risankizumab. Both agents have independently demonstrated efficacy in the treatment of CD.[1-3] However, their relative efficacy and safety are unknown owing to lack of head-to-head trials.

At DDW 2025, Rahul S. Dalal, MD, MPH, and colleagues presented results of a real-world retrospective analysis comparing the effectiveness and safety of upadacitinib and risankizumab in patients with CD receiving care in a large urban academic health system (Table 1).[4] Investigators used statistical tools, including inverse probability of treatment-weighted Cox and logistic regression with *a priori*–selected covariates, to account for differences in baseline disease severity between groups.

The cohort included 219 patients who started either upadacitinib (n=67) or risankizumab (n=152) in 2023. Most baseline characteristics were similar between arms, although patients receiving upadacitinib were younger than those receiving risankizumab, with a median age of 34 years and 42 years, respectively (*P*<.01). Sex, median disease duration, race/ethnicity, median body mass index, smoking status, and most CD characteristics were similar between groups.

There was a trend toward a higher proportion of ileal CD in the risankizumab cohort vs the upadacitinib cohort (21.7% vs 9.0%), although this did not reach statistical significance. Patients receiving upadacitinib were more likely than patients receiving risankizumab to have received prior anti–tumor necrosis factor (TNF) therapies (*P*<.01), prior ustekinumab (*P*<.01), and prior risankizumab (*P*<.01). Baseline corticosteroid use was similar between groups.

Rates of active endoscopic inflammation were similar between groups, as were imaging findings within the past year. In the subset of patients with data available, median C-reactive protein (CRP) was higher in the upadacitinib group vs the risankizumab group (6.2 vs 3.5 mg/L; *P*=.01), as was the median Harvey-Bradshaw Index (HBI) (9 vs 6; *P*=.02).

In unadjusted analyses, no significant differences between groups were noted for rates of clinical response at 12 weeks and 52 weeks, steroid-free clinical remission (SFCR; defined as HBI <5 with no use of oral corticosteroids at follow-up or physician global assessment at 52 ± 4 weeks) at 12 weeks and 52 weeks, and rates of clinical, endoscopic, and radiologic response at 52 weeks.

Investigators reported a significant difference between groups in time to treatment discontinuation within 52 weeks, with 34% of patients discontinuing upadacitinib vs 15% of patients discontinuing risankizumab (*P*<.01). Upadacitinib was also associated with higher rates of surgery within 52 weeks (9% vs 3%; *P*<.01) and adverse events (AEs) within 52 weeks (38.8% vs 19.7%; *P*<.01).

Treatment discontinuations through 52 weeks remained more frequent with upadacitinib vs risankizumab after adjusting for competing events; these included discontinuations owing to any cause (weighted hazard ratio [HR], 3.2; 95% CI, 1.7-6.0) and those specifically owing to nonresponse (*P*<.01). Exploratory Cox and logistic regression analyses found no significant difference between groups in SFCR rates at 52 weeks or in treatment discontinuation rates after excluding TNF-naive patients. Adding baseline CRP and HBI scores also did not change the findings.

AE profiles were as expected with these agents, with upadacitinib

Table 1. 1-Year Comparative Effectiveness and Safety of Upadacitinib vs Risankizumab for CD

Unadjusted outcomes	Proportion of participants	
	Upadacitinib	Risankizumab
Clinical response[a]		
12 weeks	71% (46/65)	68% (104/152)
52 weeks	67% (37/55)	79% (107/136)
Steroid-free clinical remission		
12 weeks	37% (24/65)	32% (49/152)
52 weeks	42% (23/55)	50% (68/136)
Endoscopic response[b] within 52 weeks	45% (9/20)	65% (37/57)
Radiologic response within 52 weeks	18% (4/22)	29% (14/49)
Treatment discontinuation within 52 weeks	34% (23/67)	15% (23/152)
Surgery within 52 weeks	9% (6/67)	3% (4/152)
Adverse event within 52 weeks	38.8% (26/67)	19.7% (30/152)

CD, Crohn's disease; HBI, Harvey-Bradshaw Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.
[a]Clinical response: reduction of HBI by ≥3 points.
[b]Endoscopic response: SES-CD reduction by 50%.
Adapted from Dalal RS et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract 269.[4]

yielding higher rates of several AEs, including rash.

Investigators concluded that risankizumab and upadacitinib appeared to yield similar SFCR rates. Risankizumab may provide a more durable therapy, but residual confounding factors and higher disease severity among patients receiving upadacitinib could have contributed to this difference. Thus additional study is warranted to further compare the effectiveness of these agents.

Comparative effectiveness and safety, especially of 2 newer highly effective therapies, is an important clinical inquiry. This single-center retrospective study comparing upadacitinib and risankizumab in 219 patients with CD found higher treatment failure with upadacitinib, but similar steroid-free remission rates. Despite offering early real-world data, its interpretation is limited because of imbalances in baseline characteristics, small sample size (of upadacitinib patients), underreporting of objective markers, and single-center design. Larger prospective multicenter trials are needed to clarify their comparative effectiveness, especially in treatment-refractory patient populations.

—Remo Panaccione, MD, FRCPC

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Corticosteroid-Sparing Effects of Treatment With Guselkumab in Patients With Moderately to Severely Active CD: Phase 3 GRAVITI Study Results Through Week 48

The IL-23 inhibitor guselkumab received US Food and Drug Administration (FDA) approval in March 2025 for the treatment of moderately to severely active CD after demonstrating efficacy and safety in the randomized, phase 3 GRAVITI trial.[1,2] In that trial, subcutaneous (SC) guselkumab was effective in patients with moderately to severely active CD, demonstrating superiority over placebo in week 12 clinical response rate (56.1% vs 21.4%; *P*<.001) and endoscopic response rate (41.3% vs 21.4%; *P*<.001), with no increase in AE rate.[2]

At DDW 2025, Bruce E. Sands, MD, MS, and colleagues presented results from the GRAVITI trial through week 48 (Table 2).[3] GRAVITI enrolled patients with moderately to severely active CD, defined as a Crohn's Disease Activity Index (CDAI) score of 220 to 450 and either a mean daily stool frequency count of at least 4 or an abdominal pain score of at least 2, and a Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 6, or at least 4 for isolated ileal disease. Patients were also required to have an inadequate response or intolerance to oral corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, or biologic therapy (TNF antagonists or vedolizumab).

Patients were assigned 1:1:1 to guselkumab 400 mg SC every 4 weeks (q4w) for 12 weeks followed by guselkumab 200 mg SC q4w (n=115), guselkumab 400 mg q4w for 12 weeks followed by guselkumab 100 mg SC every 8 weeks (q8w) (n=115), or placebo SC q4w (n=117). Patients in the placebo arm could receive rescue guselkumab 400 mg SC q4w for 12 weeks followed by 100 mg SC q8w. Stratification was based on CDAI (≤300 or >300), SES-CD (≤12 vs >12), and response to prior biologic.

The mean age of enrolled patients was 37.5 years and 58.5% were male; the median duration of CD was 8.0 years, mean CDAI was 296.9, and mean SES-CD was 12.0. At baseline,

nearly one-half of patients (46.4%) were biologic-naive; 68.3% were receiving at least 1 medication for CD, and 29.7% were receiving oral corticosteroids.

Among the subset of patients receiving corticosteroids at baseline, 81.6% of those patients in the guselkumab 200 mg q4w arm were able to stop corticosteroids by week 48, compared with 62.5% of those patients in the guselkumab 100 mg SC q8w arm and 18.2% of those patients in the placebo arm.

Week 48 clinical remission rates were also higher in the guselkumab arms, at 66.1% with 200 mg q4w and 60.0% with 100 mg q8w, compared with 17.1% with placebo. The pro-

The GRAVITI study found that SC guselkumab induction followed by maintenance provides robust steroid-sparing efficacy in moderate-to-severe CD. At week 48, over 80% of patients on 200 mg every 4 weeks were corticosteroid-free, with nearly two-thirds maintaining this status for 90 days. The durability and convenience of guselkumab make it a promising, practice-changing therapy, especially in resource-limited settings or for those preferring SC options. Its favorable profile may position it as a cornerstone of long-term CD care.

—Remo Panaccione, MD, FRCPC

Table 2. Corticosteroid-Sparing Effects of Treatment With Guselkumab in Patients With Moderately to Severely Active CD

Parameter	Proportion of participants		
	Placebo	Guselkumab 400 mg SC q4w→ 100 mg SC q8w	Guselkumab 400 mg SC q4w→ 200 mg SC q4w
Participants receiving corticosteroids at baseline			
Not receiving corticosteroids at week 48	18.2% (6/33)	62.5% (20/32)	81.6% (31/38)
Not receiving corticosteroids for ≥90 days prior to week 48	18.2% (6/33)	59.4% (19/32)	81.6% (31/38)
90-day corticosteroid-free clinical remission[a]	15.2% (5/33)	46.9% (15/32)	71.1% (27/38)
90-day corticosteroid-free endoscopic response[b]	3.0% (1/33)	46.9% (15/32)	50.0% (19/38)
90-day corticosteroid-free endoscopic remission[c]	3.0% (1/33)	34.4% (11/32)	39.5% (15/38)
90-day corticosteroid-free deep remission[d]	3.0% (1/33)	25.0% (8/32)	39.5% (15/38)
All participants			
Clinical remission[a]	17.1% (20/117)	60.0% (69/115)	66.1% (76/115)
90-day corticosteroid-free clinical remission	16.2% (19/117)	58.3% (67/115)	65.2% (75/115)
Endoscopic response[b]	6.8% (8/117)	44.3% (51/115)	51.3% (59/115)
90-day corticosteroid-free endoscopic response[b]	6.8% (8/117)	44.3% (51/115)	49.6% (57/115)
Endoscopic remission[c]	6.0% (7/117)	30.4% (35/115)	38.3% (44/115)
90-day corticosteroid-free endoscopic remission[c]	6.0% (7/117)	30.4% (35/115)	36.5% (42/115)
Deep remission[d]	4.3% (5/117)	26.1% (30/115)	33.9% (39/115)
90-day corticosteroid-free deep remission[d]	4.3% (5/117)	26.1% (30/115)	33.0% (38/115)

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease.
[a]Clinical remission: CDAI <150.
[b]Endoscopic response: ≥50% improvement from baseline in SES-CD.
[c]Endoscopic remission: SES-CD ≤4 and ≥2-point reduction from baseline, with no subscore >1 in any individual component.
[d]Deep remission: clinical remission and endoscopic remission.
Adapted from Hart A et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract 914.[3]

ABSTRACT SUMMARY Risankizumab Improves Symptoms in Adults With CD in Clinical Practice: Initial Results From the ASPIRE-CD Study

Charabaty and colleagues presented initial results from the prospective, observational ASPIRE-CD patient survey study that evaluated the real-world effectiveness of risankizumab in patients with moderately to severely active CD (Abstract Tu1903). Of 467 patients enrolled, 286 completed baseline surveys and started risankizumab, 241 completed week 12 surveys, and 234 continued risankizumab. Patient Global Impression of Severity had improved significantly by week 4 ($P<.01$) and continued to improve through week 12 ($P<.001$). Improvements in Patient Global Impression of Change in overall CD symptoms were also noted at weeks 4 and 12. Starting as early as week 2, patients reported improvements in abdominal pain, stool frequency, and bowel urgency that continued through week 12. Patients also reported significant reductions in corticosteroid use by week 12 ($P<.001$).

portion of patients attaining 90-day corticosteroid-free clinical remission was also higher in both guselkumab arms than with placebo, both in the overall population (65.2%, 58.3%, and 16.2%, respectively) and in the subgroup of patients receiving corticosteroids at baseline (71.1%, 46.9%, and 15.2%, respectively).

Week 48 endoscopic outcomes were also superior with guselkumab vs placebo, including the proportion of patients with endoscopic remission (38.3% with guselkumab 200 mg q4w, 30.4% with guselkumab 100 mg q8w, and 6.0% with placebo), the proportion of patients attaining 90-day corticosteroid-free endoscopic remission (36.5%, 30.4%, and 6.0%, respectively), and the proportion of patients attaining 90-day corticosteroid-free endoscopic remission after having received corticosteroids at baseline (39.5%, 34.4%, and 3.0%, respectively).

The proportion of patients attaining deep remission, defined as a clinical and endoscopic remission, was also higher with guselkumab (33.9% and 26.1%) vs placebo (4.3%). Finally, nearly all patients in the guselkumab arms who attained clinical remission, endoscopic response, or endoscopic remission were corticosteroid-free for at least 90 days.

The investigators concluded that SC guselkumab induction and maintenance therapy yielded corticosteroid-free clinical and endoscopic outcomes in patients with moderately to severely active CD.

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Comparative Effectiveness of Risankizumab Versus Ustekinumab in Bio-naive CD Patients: A Real-World Multicenter Retrospective Cohort Study

Risankizumab and ustekinumab are both monoclonal antibodies that inhibit IL-23; ustekinumab binds the p40 subunit and risankizumab binds the p19 subunit. In the SEQUENCE trial involving patients previously treated with anti-TNF therapy, risankizumab demonstrated noninferiority to ustekinumab in week 24 clinical remission rates and superiority over ustekinumab in week 48 endoscopic remission rates.[1] The relative efficacy of risankizumab and ustekinumab in anti-TNF-naive patients has not been well defined, nor has the relative efficacy of risankizumab and ustekinumab with the use of ustekinumab dose optimization.

At DDW 2025, Mohammad Aldiabat, MD, and colleagues presented results of a real-world retrospective cohort study comparing the effectiveness of risankizumab and ustekinumab in biologic-naive patients both overall and among patients receiving ustekinumab every 4 to 6 weeks (Table 3).[2] The study sample included patients from the TriNetX collaborative network, a group of 68 institutions in the United States, who had started treatment with risankizumab (n=1633) or ustekinumab (n=3106) between June 17, 2022, and October 31, 2024.

Investigators used 1:1 propensity score matching (PSM) to adjust for differences in demographics, comorbidities, parameters of CD severity, extraintestinal manifestations, concurrent corticosteroid use, hemoglobin, and body weight between groups. After this adjustment, the study group included 1562 patients in each cohort, with 640 patients in the ustekinumab every-4-to-6-week subset.

In a Cox proportional hazards model of matched cohorts, there were no differences after 1 year in key clinical outcomes including the composite outcome of need for corticosteroids, hospitalizations, emergency department

Table 3. Comparative Effectiveness of Risankizumab vs Ustekinumab in Bio-naive Patients With CD

Parameter	HR (95% CI)			
	1-year follow-up		2-year follow-up	
	Risankizumab vs Ustekinumab	Risankizumab vs Ustekinumab q4-6w	Risankizumab vs Ustekinumab	Risankizumab vs Ustekinumab q4-6w
CRP >10 mg/L	1.2 (1.0, 1.5)	1.1 (0.8, 1.5)	1.1 (0.9, 1.3)	1.0 (0.7, 1.3)
Fecal calprotectin >150 μg/g	1.2 (0.9, 1.5)	0.9 (0.6, 1.4)	1.1 (0.9, 1.3)	1.0 (0.8, 1.4)
Opioid use	1.1 (1.0, 1.3)	1.0 (0.8, 1.2)	1.1 (1.0, 1.2)	0.9 (0.7, 1.0)
Switch to advanced therapy[a]	1.1 (0.9, 1.5)	1.1 (0.8, 1.7)	1.1 (0.9, 1.4)	0.9 (0.7, 1.3)
CD-related surgery	1.3 (0.9, 1.8)	1.3 (0.8, 2.3)	1.2 (0.9, 1.7)	1.2 (0.8, 1.9)
Emergency department visit	1.1 (0.9, 1.3)	1.0 (0.7, 1.5)	1.1 (0.9, 1.3)	1.1 (0.8, 1.4)
Hospitalizations	1.1 (0.9, 1.3)	1.0 (0.7, 1.4)	0.9 (0.8, 1.1)	1.1 (0.8, 1.4)
Corticosteroids	1.1 (1.0, 1.3)	1.0 (0.8, 1.1)	1.1 (1.0, 1.2)	1.0 (0.9, 1.2)
Composite	1.1 (1.0, 1.2)	1.0 (0.8, 1.1)	1.1 (1.0, 1.2)	1.0 (0.9, 1.2)

CD, Crohn's disease; CRP, C-reactive protein; HR, hazard ratio; q4-6w, every 4 to 6 weeks.
[a]Different advanced therapy at 2-year follow-up.
Adapted from Aldiabat M et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract 123.[2]

(ED) visits, and surgeries (HR, 1.11; *P*=.06) or in individual outcomes including corticosteroid use, CD-related surgery, hospitalization, ED visits, opioid use, or a switch to advanced therapy. Similarly, there were no differences in markers of disease progression, including CRP greater than 10 mg/L or fecal calprotectin (FCP) greater than 150 μg/g.

In the subset analysis, investigators also found no significant differences in these outcomes with risankizumab compared with ustekinumab administered every 4 to 6 weeks. Two-year outcomes similarly found no significant differences in any of these outcomes either overall or among the subset of patients receiving ustekinumab every 4 to 6 weeks.

Most experts would favor anti-IL-23 therapy over anti-IL-12/23 therapy given the balance of existing evidence. This large, multicenter retrospective study comparing risankizumab and ustekinumab, including dose-optimized ustekinumab, in bio-naive CD found no significant differences in 1-year outcomes. However, limitations such as reliance on proxy measures, inconsistent coding, lack of clinical granularity, and lack of data on dosing adherence and objective disease activity warrant cautious interpretation. This study should be viewed as hypothesis generating, pending validation in prospective clinically detailed studies.

—Remo Panaccione, MD, FRCPC

Researchers noted multiple limitations of the analysis, including its observational nature, a lack of endoscopic or histologic healing data, a lack of data on treatment adherence or provider practice patterns, use of laboratory values to infer disease severity, lack of specificity in reasons for ED use and hospitalizations, and the lack of capturing risankizumab dose optimization to every 4 to 6 weeks.

The researchers concluded that their analysis revealed no differences in clinical remission rates or markers of CD progression in biologic-naive patients receiving risankizumab or ustekinumab, including dose-optimized ustekinumab, at either 1 or 2 years of follow-up. They added that ustekinumab remains a viable alternative in patients with CD not previously treated with advanced therapies.

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Low Remission Recapture After Ustekinumab Dose Optimization in CD: Results of the Randomized Placebo-Controlled Double-Blind REScUE Study

Retrospective studies have shown the possibility of recapturing responses in patients with CD with a secondary loss of response to ustekinumab.[1,2] However, this had not been prospectively evaluated.

At DDW 2025, Peter Bossuyt, MD, PhD, and colleagues presented results of the prospective double-blind, randomized, placebo-controlled REScUE study, which evaluated 2 different ustekinumab reinduction regimens in patients with CD with a documented primary response to ustekinumab who also developed secondary loss of response, defined by Patient-Reported Outcome 2 (abdominal pain score >1 and liquid or very soft stool frequency >3) and confirmed by either a biomarker increase (CRP >5 mg/L or FCP >250 µg/mg) or endoscopic relapse (Table 4).[3]

A total of 108 patients received a single intravenous (IV) dose of ustekinumab reinduction (6 mg/kg), then were randomly assigned to blinded maintenance ustekinumab 90 mg SC q4w (n=54) or ustekinumab 90 mg SC q8w (n=54) for 48 weeks. The median age of enrolled patients was 40 to 41 years; 62% were female and the median disease duration was 12 to 14 years (range, 7-23 years). Prior anti-TNF treatment had been administered to 92% of patients.

The trial did not meet its primary endpoint, demonstrating no significant difference in the proportion of patients with steroid-free clinical remission at week 48 with maintenance ustekinumab q4w compared with q8w (17% vs 16%; *P*=.96). Other week 48 endpoints were also not significantly different with q4w vs q8w dosing, including endoscopic remission rates (SES-CD <3 [10% vs 6%; *P*=.52]), endoscopic response rates (>50% decrease in SES-CD from baseline [22% vs 12%; *P*=.23]) and biomarker remission rates (CRP <5 mg/L and FCP <250 µg/g [38% vs 26%; *P*=.29]). The time to first clinical remission was not significantly difference between arms (*P*=.82). Ustekinumab serum concentrations increased significantly after IV reinduction, but higher concentrations were not associated with more favorable outcomes.

The investigators concluded that,

> The RESCUE study found that intensified ustekinumab dosing (90 mg every 4 weeks) offered no clinical benefit over the standard 8-week regimen in CD with secondary loss of response. At week 48, steroid-free remission rates and endoscopic or biomarker outcomes showed no significant differences. Given similar findings in other studies that dose intensification offers no meaningful clinical benefit, routine clinical practice of ustekinumab dose optimization should be reconsidered in favor of more effective treatment strategies.
>
> —Remo Panaccione, MD, FRCPC

Table 4. Ustekinumab Dose Optimization in CD With Secondary Loss of Response

	Proportion of participants		
Endpoint	**Ustekinumab 90 mg q4w**	**Ustekinumab 90 mg q8w**	***P* value**
Steroid-free clinical remission[a]	17% (9/54)	16% (8/54)	*P*=.96
Endoscopic remission[b]	10% (5/54)	6% (3/54)	*P*=.52
Endoscopic response[c]	22% (11/54)	12% (6/54)	*P*=.23
Biomarker remission[d]	38% (20/54)	26% (13/54)	*P*=.29

AP, abdominal pain score; CD, Crohn's disease; CRP, C-reactive protein; FCP, fecal calprotectin; PRO2, Patient-Reported Outcome 2; q4w, every 4 weeks; q8w, every 8 weeks; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.

[a]Steroid-free clinical remission: PRO2 (AP ≤1 and SF ≤3) and FCP <250 µg/g and no steroid for 90 days prior to week 48.

[b]Endoscopic remission: SES-CD <3 at week 48.

[c]Endoscopic response: 50% decrease in SES-CD compared to baseline at week 48.

[d]Biomarker remission: CRP <5 mg/L and FCP <250 µg/g at week 48.

Adapted from Bossuyt P et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract 627.[3]

in patients with CD with secondary loss of response to ustekinumab, dose optimization recaptured remission in fewer than 20% of patients. Although there was no significant difference in outcomes with q4w dosing vs q8w dosing after 1 IV reinduction infusion, the q4w regimen was numerically more effective.

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ABSTRACT SUMMARY Real-World Comparative Effectiveness of Risankizumab Versus Ustekinumab in Bio-exposed CD: A Multicenter Retrospective Cohort Analysis

Aldiabat and colleagues presented a multicenter, retrospective, real-world analysis comparing the effectiveness of risankizumab and ustekinumab in patients previously treated with biologics (Abstract Tu1860). In a PSM analysis including 946 patients, risankizumab was associated with more favorable outcomes than ustekinumab at 2 years as assessed by a composite endpoint of steroids, hospitalization, ED visits, and surgeries (HR, 0.86; *P*=.01). Among 668 patients who had received 1 prior biologic, there was only a marginal benefit with risankizumab vs ustekinumab in the composite endpoint at 1 year (HR, 0.86; *P*=.05). No composite difference between treatments was noted in the 218 patients who received 2 or more prior biologics. Among 752 patients who had received prior anti-TNF agents, the composite endpoint favored risankizumab over ustekinumab at 1 and 2 years (HR, 0.83; *P*=.01). Investigators concluded that, among patients with CD previously treated with a biologic, risankizumab provided advantages over ustekinumab at 2 years, reducing overall disease burden.

Dual-Targeted Therapy With Risankizumab and Upadacitinib Is Clinically and Biochemically Effective in Medically Complex CD

Dual targeted therapy, in which multiple targeted agents are used that inhibit different inflammatory pathways, has been evaluated as a strategy for patients with CD that is refractory to single-agent therapy and for patients with concomitant inflammatory conditions that are not addressed with their current therapy. A small retrospective study has previously demonstrated efficacy with the combination of ustekinumab and upadacitinib in patients with medically complex CD.[1] At DDW 2025, Evan N. Fear, BS, and colleagues presented results of a retrospective analysis of a prospective real-world database evaluating risankizumab plus upadacitinib in 19 patients with medically complex CD who received the combination regimen at the University of Chicago between November 2021 and September 2024 (Table 5).[2]

The median age of enrolled patients was 38 years (IQR, 33.5-43.5

Interest in advanced combination therapy for inflammatory bowel disease is growing, although research remains limited to small cohorts (except the VEGA study in ulcerative colitis). This small real-world experience using risankizumab and upadacitinib combination therapy in refractory CD showed promising clinical and biochemical improvements in highly treatment-experienced patients. Importantly, it was well tolerated with minimal discontinuation owing to AEs. High remission and response rates, despite prior biologic failure and surgical history, underscore the potential of this combination approach, reinforcing the need for prospective controlled studies to validate its efficacy and safety.

—Remo Panaccione, MD, FRCPC

Table 5. Effectiveness and Safety Outcomes of Combination Therapy With Risankizumab and Upadacitinib in Medically Complex CD

Case	Outcome	AE	Continued combination	Follow-up period (days)
1[a]	Active (clinical and biochemical)	Fatigue, upper respiratory infection	No	182
2	Active (clinical), remission (biochemical)	Nausea	Yes	509
3	Remission (clinical)	Acne, tinnitus	No	52
4	Response (clinical), remission (biochemical)	Gastrointestinal bleed	Yes	447
5	Remission (clinical, biochemical), active (erythema nodosum)	Fatigue, acne	No	196
6	Remission (clinical)	Fatigue	No	101
7[a]	Remission (clinical and biochemical)	None	Yes	307
8	Remission (clinical and biochemical)	Acne	Yes	303
9	Remission (clinical and biochemical)	Gastrointestinal bleed	Yes	473
10	Remission (clinical and biochemical)	None	Yes	219
11[a]	Remission (clinical and biochemical, peristomal pyoderma gangrenosum)	Increased hair loss	Yes	302
12	Remission (clinical and biochemical), improved arthritis	Ileocecectomy	Yes	636
13[a]	Active (clinical), remission (biochemical)	Acne	Yes	553
14	Response (clinical), active (arthritis)	Fatigue, migraines	Yes	450
15	Remission (clinical and biochemical)	Viral infection (COVID)	Yes	176
16	Remission (biochemical, psoriasis)	Small bowel obstruction	Yes	1048
17[a]	Active (gluteal/parasacral hidradenitis supprativa)	Elevated liver enzymes	No	87
18	Remission (clinical)	Injection site reaction	No	33
19	Remission (clinical and biochemical), response (psoriasis)	Viral infection (COVID)	Yes	490

AE, adverse event; CD, Crohn's disease.
[a]Ostomy patient.
Adapted from Fear EN et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, CA, USA. Abstract Tu1912.[2]

years); 68% were female, the median disease duration at initiation of dual therapy was 14.1 years, and patients had received a median of 5 prior advanced therapies. Most patients (73.7%) had undergone prior inflammatory bowel disease surgeries, including 5 ileostomies (26.3%). CD was clinically active at baseline, as assessed by HBI, in 58.3% of patients.

Among patients with active disease, risankizumab and upadacitinib was associated with a clinical remission (HBI ≤4) rate of 71.4% and a clinical response (HBI change of ≥3 from baseline) rate of 10.5%. All 4 patients with ostomies had a clinical response, and 2 achieved clinical remission. Biochemical remissions were attained in all 5 patients with active disease determined by FCP (<150 µg/g) and in 6 of 7 patients with active disease determined by CRP (<5 mg/L). Of the 8 patients with extraintestinal manifestations at baseline, 7 had improvement and 4 had resolution of their extraintestinal manifestation. There were 3 treatment discontinuations owing to AEs, including 1 each owing to acne, fatigue, and upper respiratory tract infection.

The investigators concluded that the combination of risankizumab and upadacitinib was effective in patients with medically complex CD and was generally well tolerated.

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Long-Term Efficacy and Safety of Mirikizumab Following 104 Weeks of Continuous Treatment for CD: Results From the VIVID-2 Open-Label Extension Study

Mirikizumab is an IL-23 p19 inhibitor that received FDA approval in January 2025 for the treatment of moderately to severely active ulcerative colitis.[1] The approval was based on results of the phase 3 VIVID-1 study, in which mirikizumab demonstrated a significant improvement over placebo in 2 composite endpoints: patient-reported outcome clinical response at week 12 and endoscopic response at week 52 (38.0% vs 9.0%; *P*<.0001), and patient-reported outcome clinical response at week 12 and CDAI clinical remission at week 52 (45.4% vs 19.6%; *P*<.0001).[2]

At DDW 2025, Edward L. Barnes, MD, MPH, and colleagues presented the long-term efficacy and safety of mirikizumab in 251 patients who were randomized to mirikizumab in VIVID-1 and continued on to the open-label extension study VIVID-2 (Table 6).[3] Patients received induction therapy with mirikizumab 900 mg IV at weeks 0, 4, and 8 followed by mirikizumab SC q4w. Patients with endoscopic response at week 52 continued to receive the same dosage of mirikizumab in VIVID-2.

The VIVID-2 extension study highlights the long-term efficacy and safety of mirikizumab in moderate-to-severe CD. After 104 weeks, over 80% of patients maintained endoscopic response, and more than one-half achieved endoscopic remission. Impressively, clinical remission was sustained or newly achieved regardless of prior biologic failure. High persistence with therapy, low discontinuation, and favorable safety contrast with anti-TNF agents, possibly owing to low immunogenicity of this class. These findings underscore the importance of long-term data in guiding treatment decisions.

—Remo Panaccione, MD, FRCPC

At 104 weeks, endoscopic response was maintained in 81.8% of patients using a modified nonresponder imputation analysis or 87.6% in an observed-case analysis; endoscopic remission rates were 54.9% and 58.7% and clinical remission by CDAI was achieved in 79.0% and 84.7%, respectively. Endoscopic remission was maintained in 72.5% and 78.6% of patients who were in endoscopic remission at the end of VIVID-1 and was attained in an additional 33.3% and 35.4%, respectively. Clinical remission by CDAI was maintained by 86.9% and 92.9% of patients and was attained in an additional 55.8% and 60.8%, respectively.

Investigators reported that the efficacy of mirikizumab was generally similar regardless of prior biologic failure. During the first year of VIVID-2 (the second year of patients receiving mirikizumab), 64.3% of patients had at least 1 treatment-emergent AE, 6.8% developed a serious AE, and 2 patients (0.8%) discontinued mirikizumab owing to an AE.

The investigators concluded that the VIVID-2 extension study demonstrated the long-term efficacy of mirikizumab by clinical and

Table 6. Long-Term Efficacy of Mirikizumab Following 104 Weeks of Continuous Treatment for CD

Parameter	Proportion of participants	
	Modified nonresponder imputation approach	Observed-cases approach
Endoscopic response[a]	81.8%	87.6%
Endoscopic remission[b]	54.9%	58.7%
Clinical remission[c]	79.0%	84.7%
Corticosteroid-free clinical remission[d]	86.5%	92.6%

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.
[a]Endoscopic response: ≥50% improvement from baseline in SES-CD.
[b]Endoscopic remission: SES-CD ≤4 and ≥2-point reduction from baseline, with no subscore >1 in any individual variable.
[c]Clinical remission: CDAI <150.
[d]Clinical remission by CDAI at week 52 and corticosteroid-free from week 40 to week 52.
Adapted from Barnes EL et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Tu1814.[3]

ABSTRACT SUMMARY Superior Clinical and Endoscopic Remission Rates With Vedolizumab in Early Versus Late CD: Data From the LOVE-CD Trial

Oldenburg and colleagues presented results from the open-label, multicenter LOVE-CD trial comparing use of vedolizumab in early CD (<2 years and treatment-naive or treated with only corticosteroids and/or immunomodulators) vs late CD (>2 years and treated with immunomodulators and anti-TNF agents plus corticosteroids) (Abstract Tu1893). Baseline CDAI and SES-CD were comparable between the early-CD cohort (n=86) and the late-CD cohort (n=174). At all timepoints between weeks 6 and 52, steroid-free clinical remission rates were higher in early CD vs late CD. The proportion of patients with steroid-free deep remissions (clinical [CDAI ≤150] and endoscopic [SES-CD ≤3] remission) at weeks 26 and 52 was significantly higher in the early-CD group vs the late-CD group (31.4% vs 8.6%; *P*<.001). Individual efficacy measures were also significantly better in the early-CD group. There was no benefit with dose intensification among patients with endoscopic nonresponse at week 26.

endoscopic measures in patients with moderately to severely active CD, with many patients maintaining response and remission after 2 years and others gaining remission in the second year of treatment. Moreover, the safety outcomes were consistent with the known safety profile of mirikizumab.[2]

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Impact of Immunogenicity on 2-Year Clinical Outcomes in Patients With Moderate-to-Severe CD Treated With Subcutaneous Infliximab: A Post Hoc Analysis of the Phase 3 LIBERTY-CD Study

Several studies have demonstrated that the development of antidrug antibodies (ADAs) is associated with poorer outcomes in patients with CD receiving biologics.[1,2] However, in a post hoc analysis from the phase 3 LIBERTY-CD trial, although ADAs were associated with lower serum infliximab levels in patients receiving SC infliximab, they were not associated with drug persistence or clinical efficacy.[3]

At DDW 2025, Dr Sands and colleagues presented a post hoc analysis from LIBERTY-CD evaluating the effects of ADAs on clinical outcomes up to week 102 in patients receiving infliximab SC maintenance treatment (Table 7).[4] The analysis included 231 patients with a response to infliximab IV induction therapy at week 10 who were randomly assigned to receive infliximab SC in the LIBERTY-CD trial. Patients were categorized as

Table 7. Efficacy Outcomes at Week 102 by ADA Titer Level in Patients With Moderate-to-Severe CD Treated With Subcutaneous Infliximab

Parameter	ADA titer level			
	Negative	Low	Moderate	High
Clinical remission,[a] proportion of patients	46.6% (27/58)	69.7% (23/33)	58.3% (28/48)	37.5% (9/24)
Endoscopic response,[b] proportion of patients	50.0% (29/58)	57.6% (19/33)	43.8% (21/48)	8.3% (2/24)
CDAI, mean score	68.8	58.4	67.8	91.0
SES-CD, mean score	2.5	3.5	2.6	7.3

ADA, anti-drug antibody; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.
[a]Clinical remission: CDAI <150.
[b]Endoscopic response: ≥50% reduction from SES-CD at baseline.
Adapted from Sands BE et al. Presented at: DDW 2025; May 3-6, 2025; San Diego, California, USA. Abstract Su1842.[4]

ADA-positive (ADAs were detected at any point after treatment initiation) or ADA-negative (ADAs were not detected at any point). PSM was used to balance the ADA-positive and ADA-negative groups 2:1. The PSM cohort included 105 patients in the ADA-positive group and 58 patients in the ADA-negative.

At week 102, there was no significant difference in any efficacy outcome between ADA-positive and ADA-negative groups, including clinical remission rate, endoscopic response rate, CDAI, or SES-CD, whether data were analyzed as observed or with missing data imputed as nonremitter or nonresponder. No differences in drug persistence between the ADA-positive and ADA-negative groups were observed up to week 102. However, mean serum infliximab levels during the maintenance phase were lower in ADA-positive vs ADA-negative patients.

Outcomes were also assessed by ADA titer level. Week 102 efficacy was comparable between ADA-positive and ADA-negative groups in patients with low-to-moderate ADA titer levels. A high ADA titer (≥1000) was associated with lower rates of endoscopic response and higher SES-CD. Drug persistence was significantly lower among patients with high ADA titers compared with patients with low ADA titers. Moreover, mean serum infliximab levels during the maintenance phase were consistently lower in the high-titer group than the ADA-negative group and other subgroups.

The investigators concluded that the development of ADAs in patients receiving infliximab SC maintenance therapy did not significantly affect clinical outcomes or drug persistence up to week 102 except in patients with an ADA titer of 1000 or greater, in whom endoscopic response rates were lower and serum drug levels were lower. They added that this analysis was based on a newly developed electrochemiluminescence affinity capture elution assay, and thus additional studies are needed to further assess absolute threshold titers that affect outcomes and to relate the findings to other ADA assay types.

This post hoc analysis of the LIBERTY-CD trial examined the long-term impact of ADAs on SC infliximab levels and outcomes in CD. At week 102, ADA positivity did not significantly affect drug persistence or clinical and endoscopic outcomes. However, very high ADA titers (>1000) were associated with reduced endoscopic response rates. These findings suggest that, although low-titer ADAs may not compromise long-term efficacy, high titers could impair mucosal healing, reinforcing the importance of ADA titer monitoring in anti-TNF therapy management.

—Remo Panaccione, MD, FRCPC

ABSTRACT SUMMARY Risankizumab Versus Anti-TNF-α Agents in CD: Comparative Impact on Corticosteroid Dependency Over 24 Months

Sawaf and colleagues presented results of a retrospective cohort analysis comparing the effectiveness of risankizumab vs anti-TNF agents for reducing corticosteroid dependency and hospitalization rates at 12 and 24 months in patients with CD (Abstract Tu1855). The study included 3146 patients treated 1:1 with risankizumab or anti-TNF agents. Use of risankizumab was associated with a significantly reduced risk of receiving oral corticosteroids compared with use of anti-TNF agents at 12 months (odds ratio, 0.63; 95% CI, 0.53-0.74; *P*<.001) and at 24 months (odds ratio, 0.59; 95% CI, 0.48-0.71; *P*<.001). There was no significant difference in rates of IV corticosteroid use at 12 or 24 months.

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CROHN'S DISEASE 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. Patients received an IV infusion of SKYRIZI 600 mg (recommended dose), risankizumab-rzaa 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]

FORTIFY OLE: An ongoing, multicenter, open-label extension of Phase 3 studies evaluating the long-term efficacy and safety of SKYRIZI 180 mg SC. Patients who achieved clinical response in ADVANCE or MOTIVATE at Week 12 and completed the 52-week FORTIFY maintenance period were eligible to participate.[3]

INDICATION[1]

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

SAFETY CONSIDERATIONS[1]

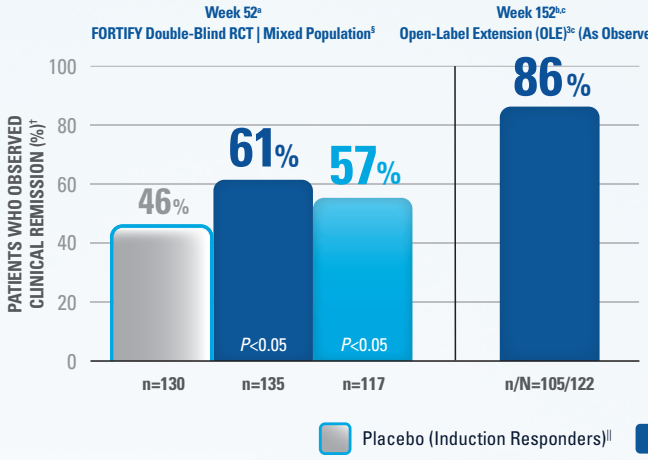
SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of its excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of SKYRIZI. If a serious hypersensitivity reaction occurs, discontinue SKYRIZI and initiate appropriate therapy immediately. SKYRIZI may increase the risk of infection. Instruct patients to report signs or symptoms of clinically important infection during treatment. Should such an infection occur, discontinue SKYRIZI until infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with SKYRIZI. Drug-induced liver injury was reported in a patient with Crohn's disease during induction dosing of SKYRIZI. For the treatment of Crohn's disease and ulcerative colitis, evaluate liver enzymes and bilirubin at baseline and during induction (12 weeks). Interrupt treatment with SKYRIZI if drug-induced liver injury is suspected, until this diagnosis is excluded. Avoid use of live vaccines in SKYRIZI patients.

Please see additional Important Safety Information on the following page of this advertisement.

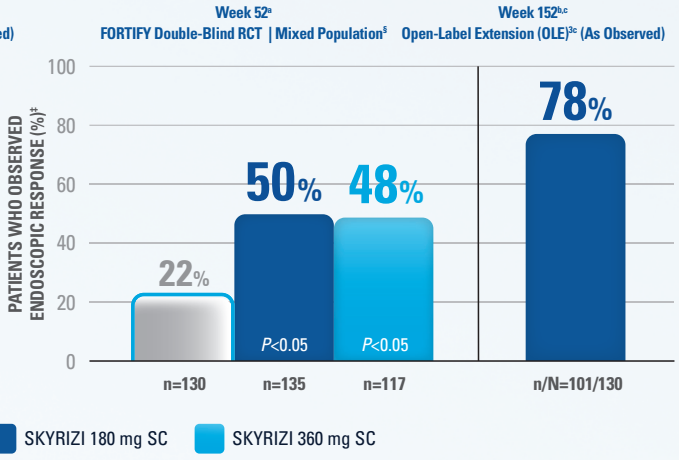
Please see Brief Summary of full Prescribing Information on adjacent pages of this advertisement.

CLINICAL REMISSION AND ENDOSCOPIC RESPONSE DATA[1,3]

Clinical Remission[†]



Endoscopic Response[‡]



Placebo (Induction Responders)[‖] | SKYRIZI 180 mg SC | SKYRIZI 360 mg SC

Use the lowest effective dosage to maintain therapeutic response.

[a]**Results at 52 weeks are among 382 patients who achieved clinical response[¶] after 12 weeks of treatment with SKYRIZI in induction trials.[1]**

[b]**OLE Limitations for Week 152 Data:** 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 the drug often drop out.

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

SYMPTOM AND ENDOSCOPIC CONTROL AT WEEK 12[1]

Clinical Remission[†] at Week 12[1]

ADVANCE | Mixed Population[§]

- **45% (n=336) SKYRIZI 600 mg IV**
- 25% (n=175) Placebo (*P*<0.001)[1]

MOTIVATE | Advanced Therapy[#]-Failure Population**

- **42% (n=191) SKYRIZI 600 mg IV**
- 20% (n=187) Placebo (*P*<0.001)

Endoscopic Response[‡] at Week 12[1]

ADVANCE | Mixed Population[§]

- **40% (n=336) SKYRIZI 600 mg IV**
- 12% (n=175) Placebo (*P*<0.001)

MOTIVATE | Advanced Therapy[#]-Failure Population**

- **29% (n=191) SKYRIZI 600 mg IV**
- 11% (n=187) Placebo (*P*<0.001)

ENDOSCOPIC REMISSION[††] DATA AT WEEKS 12, 52, AND 152[1]

Endoscopic Remission[††] at Week 12[1]

ADVANCE | Mixed Population[§]

- **24% (n=336) SKYRIZI 600 mg IV**
- 9% (n=175) Placebo (Induction Responders)[‖] (*P*<0.001)

MOTIVATE | Advanced Therapy[#]-Failure Population**

- **19% (n=191) SKYRIZI 600 mg SC**
- 4% (n=187) Placebo (Induction Responders)[‖] (*P*<0.001)

Endoscopic Remission[††] at Week 52[1a]

FORTIFY | Mixed Population[§]

- **33% (n=135) SKYRIZI 180 mg SC**
- **41% (n=117) SKYRIZI 360 mg SC**
- 13% (n=130) Placebo (Induction Responders)[‖]

Endoscopic Remission[††] at Week 152[3]

Open-Label Extension (OLE)[b,c] (As Observed)

- **64% (n/N=83/130) SKYRIZI 180 mg SC**

Use the lowest effective dosage to maintain therapeutic response.

DATA LIMITATIONS: Endoscopic remission[††] at Week 52 was not statistically significant under the pre-specified multiple testing procedure.

[a]**Results at 52 weeks are among 382 patients who achieved clinical response[¶] after 12 weeks of treatment with SKYRIZI in induction trials.[1]**

[b]**OLE Limitations for Week 152 Data:** 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 the drug often drop out.

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

[#]Advanced therapy in Crohn's is defined as biologics.

INTERESTED IN SEEING ADDITIONAL DATA?
WWW.SKYRIZIHCP.COM

Skyrizi®
risankizumab-rzaa

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 Inflammatory Bowel 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 and ulcerative colitis, 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.

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.

Most common (≥3%) adverse reactions associated with SKYRIZI in ulcerative colitis are arthralgia in induction, and arthralgia, pyrexia, injection site reactions, and rash 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. Lipid elevations observed in patients with ulcerative colitis were similar to those in Crohn's disease.

Dosage Forms and Strengths: SKYRIZI (risankizumab-rzaa) 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 Brief Summary of full Prescribing Information on adjacent pages of this advertisement.

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

‡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).[1]

§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 were bio-exposed but did not have an inadequate response, loss of response, or intolerance to biologics (advanced therapy# naïve).[1]

‖Placebo (Induction Responders): Patients who achieved CDAI clinical response (CR-100)¶ to SKYRIZI induction therapy and were randomized to receive placebo in maintenance study.[1]

¶Clinical response was defined as a reduction of CDAI score ≥100 points from baseline.

#Advanced therapy in Crohn's is defined as biologics.

**Prior advanced therapy failure includes inadequate response, loss of response, or intolerance to one or more biologics.[1]

††Endoscopic Remission: SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer.[1]

CDAI=Crohn's disease activity index; CR=clinical response; IV=intravenous; RCT=randomized clinical trial; SC=subcutaneous; SES-CD=simple endoscopic score for Crohn's disease.

References: 1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc. **2.** Data on file, AbbVie Inc. Source: Symphony Health, an ICON plc Company, IDV®; March 1, 2023-May 31, 2024. **3.** Data on file, AbbVie Inc. ABVRRTI79854.

abbvie

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.

Ulcerative Colitis

SKYRIZI is indicated for the treatment of moderately to severely active ulcerative colitis 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 Inflammatory Bowel 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 and ulcerative colitis, 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 Inflammatory Bowel 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 with Plaque Psoriasis 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 (CD-1, CD-2, and CD-4)

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 (CD-3).

Ulcerative Colitis

SKYRIZI was studied up to 12 weeks in subjects with moderately to severely active ulcerative colitis in a randomized, double-blind, placebo-controlled induction study (UC-1) and a randomized, double-blind, placebo-controlled, dose-finding study (UC-3). 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 (UC-2).

In the induction studies (UC-1 and UC-3), 712 subjects received the SKYRIZI 1,200 mg intravenous induction regimen at Weeks 0, 4 and 8. In the maintenance study (UC-2), 347 subjects who achieved clinical response, defined as a decrease in mMS of ≥2 points and ≥30% from baseline and a decrease in RBS ≥1 from baseline or an absolute RBS ≤1, 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.

The adverse reaction reported in ≥3% subjects treated with SKYRIZI in the ulcerative colitis induction studies (UC-1 and UC-3) and at a higher rate than placebo was arthralgia (3% SKYRIZI vs 1% placebo).

Adverse reactions reported in ≥3% of subjects treated with SKYRIZI in the maintenance study (UC-2) and at a higher rate than placebo are shown in Table 4.

Table 4. Adverse Reactions Reported in ≥3% of Subjects with Ulcerative Colitis Treated with SKYRIZI[a] in Placebo-Controlled 52-Week Maintenance Study (UC-2)

Adverse Drug Reactions	SKYRIZI 180 mg Subcutaneous Injection N = 170 n (%)	SKYRIZI 360 mg Subcutaneous Injection N = 177 n (%)	Placebo N = 173 n (%)
Arthralgia	9 (5.3)	17 (9.6)	8 (4.6)
Pyrexia	8 (4.7)	7 (4.0)	6 (3.5)
Injection site reactions[b,c]	5 (2.9)	5 (2.8)	2 (1.2)
Rash[d]	7 (4.1)	1 (0.6)	3 (1.7)

[a] SKYRIZI 180 mg or 360 mg at Week 12 and every 8 weeks thereafter for up to an additional 52 weeks

[b] Includes: application site pain, injection site erythema, injection site pain, injection site pruritus, injection site reaction

[c] 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.

[d] Includes: rash and rash macular

Specific Adverse Drug Reactions

The rates of infections, serious infections, and lipid elevations in subjects with UC who received SKYRIZI compared to subjects who received placebo in the induction studies (UC-1 and UC-3) and maintenance study (UC-2) were similar to the rates in subjects with CD who received SKYRIZI compared to subjects who received placebo in the induction studies (CD-1, CD-2, and CD-4) and maintenance study (CD-3).

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.

Ulcerative Colitis

By Week 64, antibodies to risankizumab-rzaa developed in approximately 8.9% (8/90) or 4.4% (4/91) of subjects treated with SKYRIZI induction followed by the 180 mg or 360 mg maintenance regimen, respectively. Of the subjects who developed antibodies to risankizumab-rzaa, 75% (6.7% of all subjects treated with SKYRIZI induction followed by the 180 mg maintenance regimen) or 50% (2.2% of all subjects treated with SKYRIZI induction followed by the 360 mg maintenance regimen), respectively, 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 5 times the exposure (AUC) in humans administered the maximum recommended induction dose (1,200 mg) and 32 times the exposure (AUC) to the maximum recommended maintenance dose (360 mg). 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 2,500 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. The 5 mg/kg dose in pregnant monkeys resulted in approximately 0.6 times the exposure (AUC) in humans administered the maximum recommended induction dose (1,200 mg) and 5 times the exposure (AUC) in humans administered the maximum recommended maintenance dose (360 mg). 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 6,862 subjects exposed to SKYRIZI, a total of 664 were 65 years or older (243 subjects with plaque psoriasis, 246 subjects with psoriatic arthritis, 72 subjects with Crohn's disease and 103 subjects with ulcerative colitis), and 71 subjects were 75 years or older.

Clinical studies of SKYRIZI, within each indication, 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 based on age.

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 Inflammatory Bowel 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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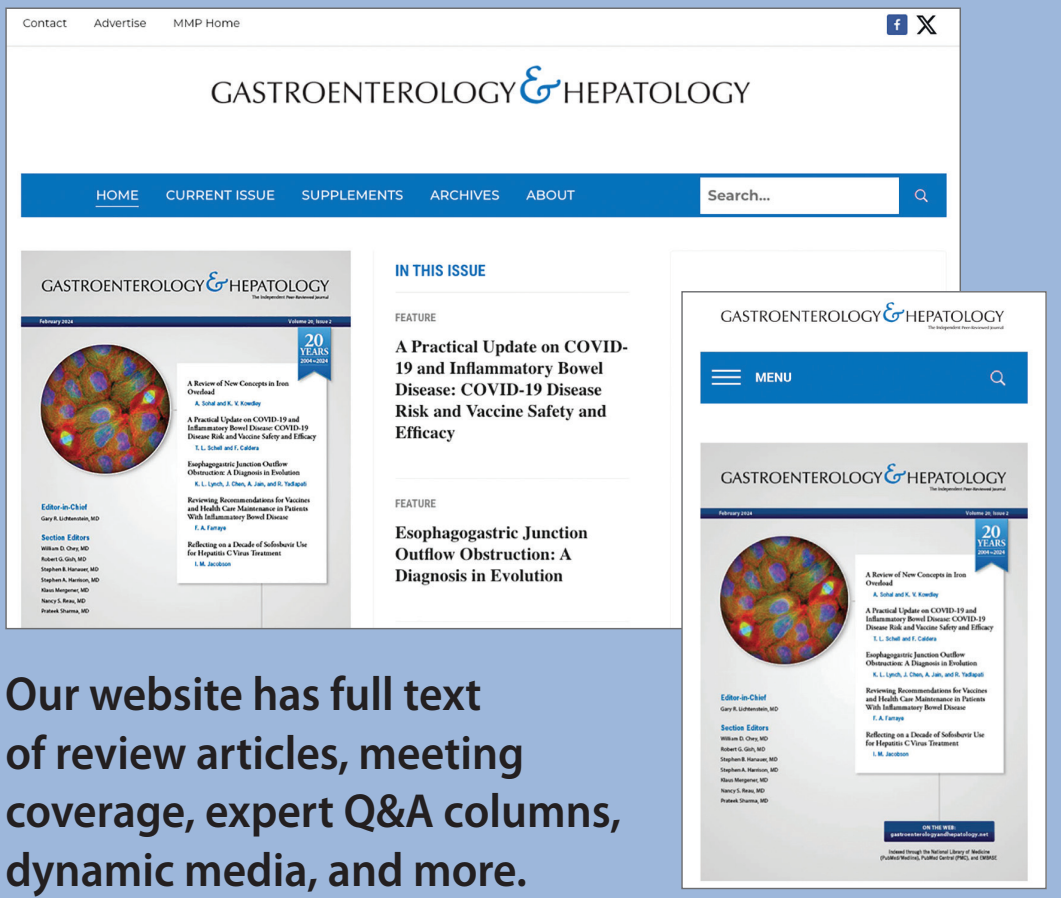

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