GASTROENTEROLOGY & HEPATOLOGY
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A SPECIAL MEETING REVIEW EDITION

Highlights in Crohn's Disease From the American College of Gastroenterology 2023 Annual Scientific Meeting

A Review of Selected Presentations From the ACG 2023 Annual Scientific Meeting • October 20-25, 2023 • Vancouver, Canada

Special Reporting on:

- Analysis of Upadacitinib in IBD: Evaluating Safety and Efficacy Across Phase 3 Trials in Patients With Crohn's Disease or Ulcerative Colitis
- Safety and Efficacy of Risankizumab in Crohn's Disease: Prospective Real-World Experience and Systematic Literature Review
- Ustekinumab Reintroduction: Week 16 Results and Baseline Response Analysis From the POWER Study in Patients With Crohn's Disease
- Efficacy and Safety of Guselkumab in Crohn's Disease: Results From the GALAXI 1 Study
- Real-World Clinical Effectiveness and Safety of Vedolizumab and Ustekinumab in Bio-naive Patients With Complex or Noncomplex Crohn's Disease: Results From the EVOLVE Expansion Study
- Safety Insights on Filgotinib in Crohn's Disease From the DIVERSITY1 and SELECTION Studies

PLUS Meeting Abstract Summaries

With Expert Commentary by:

David T. Rubin, MD
Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology, and Nutrition
Director, Inflammatory Bowel Disease Center
The University of Chicago Medicine
Chicago, Illinois

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RINVOQ®
upadacitinib

For adults with moderately to severely active Crohn's disease (CD) who have had an inadequate response or intolerance to one or more TNF blockers.[1]

PUT CROHN'S IN CHECK AND KEEP IT THERE

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

Results were measured at Weeks 12 and 52

RAPID SYMPTOM RELIEF
Clinical response* achieved at Week 2[1]

DURABLE CLINICAL REMISSION
Clinical remission† achieved at Weeks 12 and 52[1]

SIGNIFICANT ENDOSCOPIC CONTROL
Visible mucosal improvement with endoscopic response‡ achieved at Weeks 12 and 52[1]

U-EXCEL Induction & 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 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]

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.

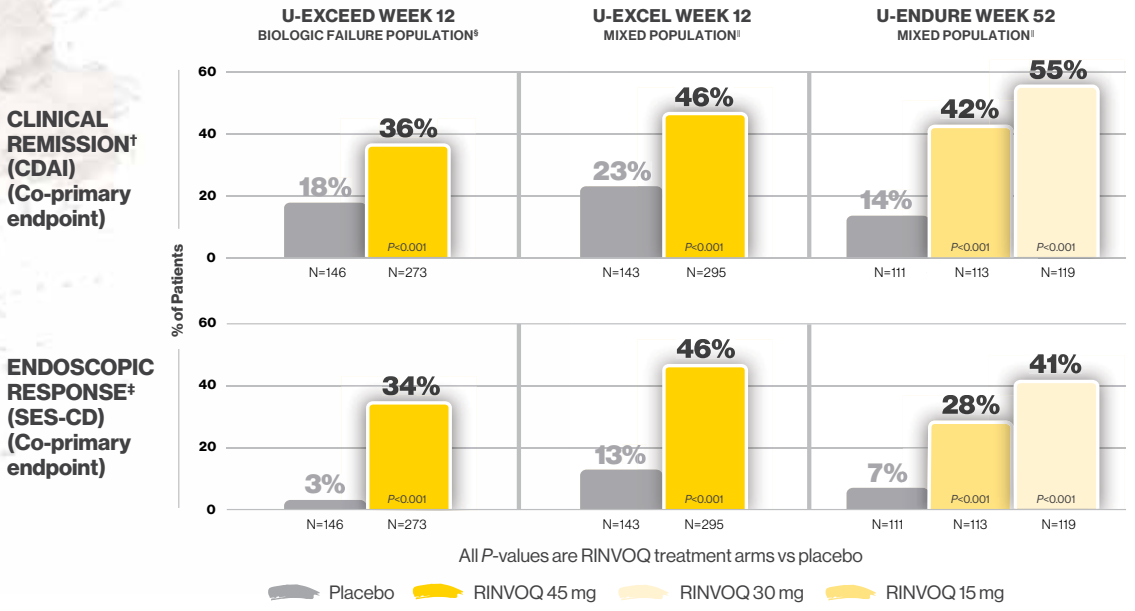
In both induction trials, ~1/3 of patients achieved rapid symptom relief (CDAI CR-100) at Week 2 (ranked secondary endpoint).[3]

U-EXCEED 37% (n=273) RINVOQ 45 mg; 14% (n=146) placebo (*P*<0.001).[3]

U-EXCEL 37% (n=295) RINVOQ 45 mg; 24% (n=143) placebo (*P*<0.01).[3]

RESULTS YOUR PATIENTS CAN FEEL AND YOU CAN SEE

Durable clinical remission† and significant endoscopic control[1‡]



RINVOQ is indicated for TNFi-IR patients.

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.

SEE MORE DATA
including steroid-free clinical remission at **RINVOQHCP.COM/CD**

CDAI=Crohn's disease activity index; SES-CD=simple endoscopic score for Crohn's disease; TNFi-IR=tumor necrosis factor inhibitor-intolerance or inadequate response.
*Clinical response was defined as a reduction of CDAI score ≥100 points from baseline.[1]
†Clinical remission was defined as CDAI <150 points.[1]
‡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]
§Prior biologic failure includes inadequate response, loss of response, or intolerance to one or more biologics.[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-naive).[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 varicella zoster or prophylactic 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.; 2023. **2.** Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. *Nat Rev Dis Primers*. 2020;6(1):22. Published 2020 Apr 2. doi:10.1038/s41572-020-0156-2. **3.** Data on File. ABVRRTI75381.

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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.

Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic 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 DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Atopic Dermatitis

RINVOQ is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

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.

Ankylosing Spondylitis

RINVOQ is indicated for the treatment of adults with active ankylosing spondylitis 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 DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Non-radiographic Axial Spondyloarthritis

RINVOQ is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, 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.

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, it is recommended that patients be brought up to date with all immunizations, including varicella zoster or prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

Medication Residue in Stool

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions

with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly. Monitor patients clinically and consider alternative treatment if there is an inadequate therapeutic response.

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Adverse Reactions in Patients with Rheumatoid Arthritis

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

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

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

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

Adverse Reaction	Placebo	RINVOQ 15 mg
	N = 1042 (%)	N = 1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2
*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection		

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

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

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

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

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

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

Specific Adverse Reactions

Infections

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

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

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

Serious Infections

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

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

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

The most frequently reported serious infections were pneumonia and cellulitis.

Tuberculosis

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

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

Opportunistic Infections (excluding tuberculosis)

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

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

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

Malignancies

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

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

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

Gastrointestinal Perforations

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

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

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

Thrombosis

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

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

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

Laboratory Abnormalities

Hepatic Transaminase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

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

1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

Lipid Elevations

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

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

Creatine Phosphokinase Elevations

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

Lymphopenia

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

Anemia

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

Adverse Reactions in Patients with Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical trials representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the two Phase 3 trials, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

Two placebo-controlled trials were integrated (640 patients on RINVOQ 15 mg once daily and 635 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 24 weeks after treatment initiation.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were ≥1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively with placebo. A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

Adverse Reactions in Patients with Atopic Dermatitis

Three Phase 3 (AD-1, AD-2, and AD-3) and one Phase 2b (AD-4) randomized, double-blind, placebo-controlled, multicenter trials evaluated the safety of RINVOQ in patients with moderate-to-severe atopic dermatitis. The majority of patients were White (68%) and male (57%). The mean age was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. In these 4 trials, 2612 patients were treated with RINVOQ 15 mg or 30 mg orally once daily, with or without concomitant topical corticosteroids (TCS).

In the Phase 3 clinical trials (AD-1, AD-2, and AD-3), a total of 1239 patients received RINVOQ 15 mg, of whom 791 were exposed for at least one year and 1246 patients received RINVOQ 30 mg, of whom 826 were exposed for at least one year.

Trials AD-1, AD-2, and AD-4 compared the safety of RINVOQ monotherapy to placebo through Week 16. Trial AD-3 compared the safety of RINVOQ + TCS to placebo + TCS through Week 16.

Weeks 0 to 16 (Trials AD-1 to AD-4)

In RINVOQ trials with and without TCS (Trials AD-1, 2, 3 and 4) through Week 16, the proportion of patients who discontinued treatment because of adverse reactions in the RINVOQ 15 mg, 30 mg and placebo groups were 2.3%, 2.9% and 3.8%, respectively. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the RINVOQ 15 mg or 30 mg groups during the first 16 weeks of treatment.

Table 2: Adverse Reactions Reported in ≥ 1% of Patients with Atopic Dermatitis Treated with RINVOQ 15 mg or 30 mg

Adverse Reaction	Placebo	RINVOQ 15 mg	RINVOQ 30 mg
	N = 902 (%)	N = 899 (%)	N = 906 (%)
Upper respiratory tract infection (URTI)*	17	23	25
Acne**	2	10	16
Herpes simplex***	2	4	8
Headache	4	6	6
Increased blood creatine phosphokinase	2	5	6
Cough	1	3	3
Hypersensitivity****	2	2	3
Folliculitis	1	2	3
Nausea	1	3	3
Abdominal pain*****	1	3	2
Pyrexia	1	2	2
Increased Weight	1	2	2
Herpes zoster******	1	2	2
Influenza	<1	2	2

Adverse Reaction	Placebo	RINVOQ 15 mg	RINVOQ 30 mg
	N = 902 (%)	N = 899 (%)	N = 906 (%)
Fatigue	1	1	2
Neutropenia	<1	1	2
Myalgia	1	1	2
Influenza like illness	1	1	2

* Includes: laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
** Includes: acne and dermatitis acneiform
*** Includes: genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes
**** Includes anaphylactic reaction, anaphylactic shock, angioedema, dermatitis exfoliative generalized, drug hypersensitivity, eyelid oedema, face oedema, hypersensitivity, periorbital swelling, pharyngeal swelling, swelling face, toxic skin eruption, type I hypersensitivity, urticaria
***** Includes abdominal pain and abdominal pain upper
****** Includes herpes zoster and varicella

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg and/or 30 mg group and at a higher rate than in the placebo group through Week 16 included anemia, oral candidiasis, pneumonia, non-melanoma skin cancer, and the adverse event of retinal detachment.

The safety profile of RINVOQ through Week 52 was generally consistent with the safety profile observed at Week 16.

Overall, the safety profile observed in patients with AD treated with RINVOQ was similar to the safety profile in patients with RA. Other specific adverse reactions that were reported in patients with AD included eczema herpeticum/Kaposi's varicelliform eruption.

Eczema Herpeticum/Kaposi's Varicelliform Eruption

Placebo-controlled Period (16 weeks): Eczema herpeticum was reported in 4 patients (1.6 per 100 patient-years) treated with placebo, 6 patients (2.2 per 100 patient-years) treated with RINVOQ 15 mg and 7 patients (2.6 per 100 patient-years) treated with RINVOQ 30 mg.

12-Month Exposure (Weeks 0 to 52): Eczema herpeticum was reported in 18 patients (1.6 per 100 patient-years) treated with RINVOQ 15 mg and 17 patients (1.5 per 100 patient-years) treated with RINVOQ 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

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

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

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

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 3 and 4, respectively.

Table 3: 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 4: Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]

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

[1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily

* Composed of several similar terms

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

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

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

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

Specific Adverse Reactions

Serious Infections

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

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

Laboratory Abnormalities

Hepatic Transaminase Elevations

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

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

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

Adverse Reactions in Patients with Crohn's Disease

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

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

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

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

Adverse reactions reported in ≥2% of patients treated with RINVOQ and at a higher rate than placebo in the induction and maintenance studies are shown in Tables 5 and 6, respectively.

Table 5: 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 6: 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.

Adverse Reactions in Patients with Ankylosing Spondylitis

A total of 596 patients with ankylosing spondylitis were treated with RINVOQ 15 mg in the two clinical trials representing 577.3 patient-years of exposure, of whom 220 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active ankylosing spondylitis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis and psoriatic arthritis. During the 14-week placebo-controlled period in Trial AS-I, the frequency of headache was 5.4% with RINVOQ 15 mg and 2.1% with placebo. During the 14-week placebo-controlled period in Trial AS-II, the frequency of headache was 3.3% with RINVOQ 15 mg and 1.4% with placebo.

Adverse Reactions in Patients with Non-radiographic Axial Spondyloarthritis

A total of 187 patients with non-radiographic axial spondyloarthritis were treated with RINVOQ 15 mg in the clinical trial representing 116.6 patient-years of exposure, of whom 31 were exposed to RINVOQ 15 mg for at least one year.

Overall, the safety profile observed in patients with active non-radiographic axial spondyloarthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors

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

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

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

Strong CYP3A4 Inducers

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Report pregnancies to the AbbVie Inc.'s Adverse Event reporting line at 1-800-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Data

Animal Data

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

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

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

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

Lactation

Risk Summary

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

Data

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

Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis have not been established.

Atopic Dermatitis

The safety and effectiveness of RINVOQ in pediatric patients 12 years of age and older weighing at least 40 kg with atopic dermatitis have been established. A total of 344 pediatric patients aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across three trials (AD-1, AD-2 and AD-3) to receive either RINVOQ 15 mg (N=114) or 30 mg (N=114) or matching placebo (N=116) in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the pediatric patients and adults. The adverse reaction profile in the pediatric patients was similar to the adults *[see Adverse Reactions]*.

The safety and effectiveness of RINVOQ in pediatric patients less than 12 years of age with atopic dermatitis have not been established.

Ulcerative Colitis and Crohn's Disease

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

Geriatric Use

Rheumatoid Arthritis and Psoriatic Arthritis

Of the 4381 patients treated in the five clinical trials, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 patients 75 years and older. Of the 1827 patients treated in the two psoriatic arthritis Phase 3 clinical trials, a total of 274 patients were 65 years of age or older, including 34 patients 75 years and older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections, in patients 65 years of age and older.

Atopic Dermatitis

Of the 2583 patients treated in the three Phase 3 clinical trials, a total of 120 patients with atopic dermatitis were 65 years of age or older, including 6 patients 75 years of age. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of serious infections and malignancies in those patients 65 years of age or older in the 30 mg dosing group in the long-term trials.

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.

Ankylosing Spondylitis

Of the 607 patients treated in the controlled clinical trials, a total of 32 patients with ankylosing spondylitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ankylosing spondylitis to determine whether they respond differently from younger adult patients.

Non-radiographic Axial Spondyloarthritis

Of the 313 patients treated in a phase 3 clinical trial, a total of 9 patients with non-radiographic axial spondyloarthritis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with non-radiographic axial spondyloarthritis to determine whether they respond differently from younger adult patients.

Renal Impairment

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

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

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

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

Hepatic Impairment

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

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

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

PATIENT COUNSELING INFORMATION

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

Serious Infections

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

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

Malignancies

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

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

Major Adverse Cardiovascular Events

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

Thrombosis

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

Hypersensitivity Reactions

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

Gastrointestinal Perforations

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

Retinal Detachment

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

Laboratory Abnormalities

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

Vaccinations

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

Embryo-Fetal Toxicity

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

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

Advise females patients who are exposed to RINVOQ during pregnancy to contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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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Analysis of Upadacitinib in IBD: Evaluating Safety and Efficacy Across Phase 3 Trials in Patients With Crohn's Disease or Ulcerative Colitis

Current research into new therapeutics for inflammatory bowel disease (IBD) focuses on targeted biologics and small molecules to attack specific molecular pathways that promote IBD pathologies. Upadacitinib is an oral, reversible inhibitor of Janus kinase (JAK) that is approved as induction or maintenance therapy for patients with moderately to severely active Crohn's disease (CD) or ulcerative colitis (UC) who have had an inadequate response to 1 or more tumor necrosis factor (TNF) inhibitors.[1,2] U-ACHIEVE and U-ENDURE, both phase 3 trials, demonstrated the superiority of upadacitinib (15 or 30 mg, daily) in comparison with placebo as maintenance therapy in patients with moderately to severely active UC or CD.[3,4] To evaluate long-term safety outcomes, investigators conducted a post hoc analysis of patient data from the 2 trials.[5] Treatment-emergent adverse events (AEs) were pooled from patients in both studies who responded to upadacitinib induction and then received placebo or upadacitinib as maintenance therapy.

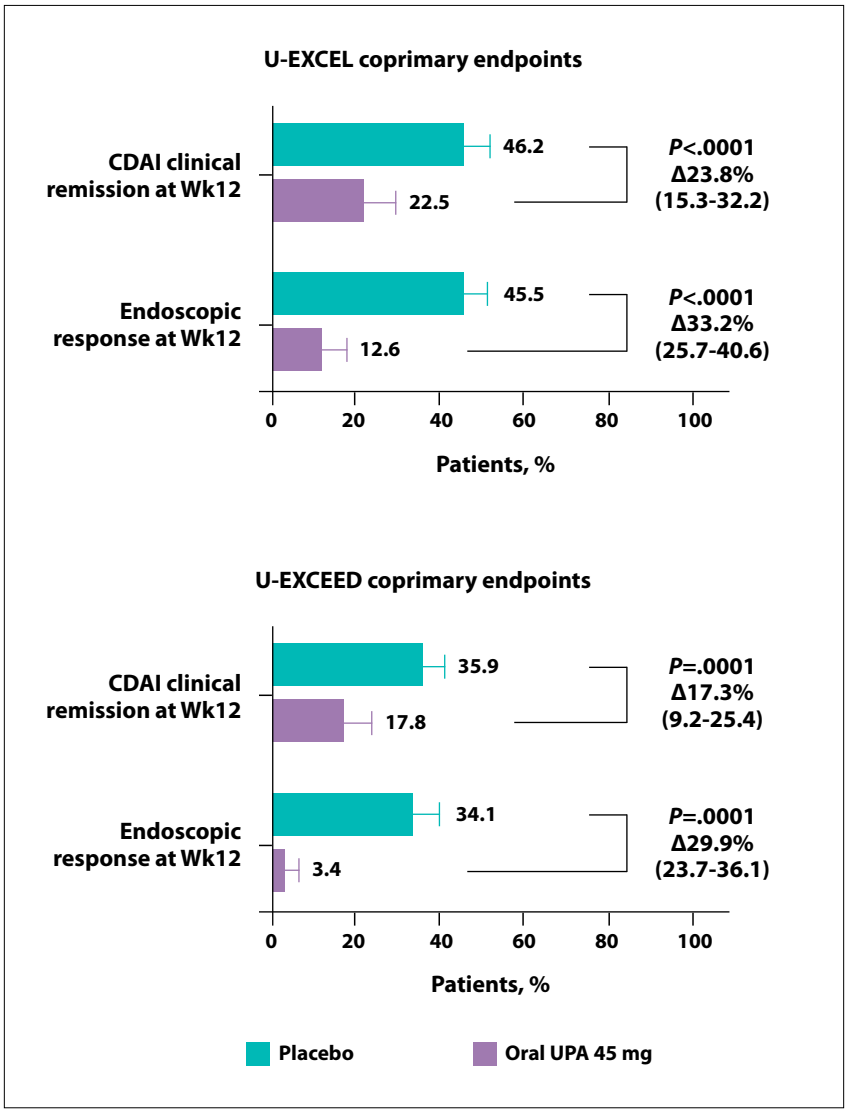

Figure 1. U-EXCEL and U-EXCEED induction results among patients with CDAI ≥220 at BL.

BL, baseline; CDAI, Crohn's Disease Activity Index; UPA, upadacitinib; wk, week.
Adapted from Rubin et al. Abstract P0732. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[6]

The analysis included 746 patients from U-ACHIEVE and 673 from U-ENDURE. In a comparison of the placebo vs the upadacitinib cohorts, the rates of serious and severe treatment-emergent AEs were higher with placebo than with upadacitinib in both patients with UC and those with CD. The most frequently reported infections were nasopharyngitis (exposure-adjusted event rate [EAER], 11.6-14.2), upper respiratory infection (EAER, 6.8-7.3), and COVID19 (EAER, 6.9-7.6). Rates of serious infections were similar across treatment groups; however, herpes zoster was more common among patients treated with upadacitinib. In each upadacitinib treatment group (15 or 30 mg; 0.3/100 patient-years), 1 gastrointestinal perforation was observed, whereas 2 perforations were observed in the placebo group. Rates of venous thromboembolism were higher with 15 mg of upadacitinib (EAER, 1.0) or 30 mg of upadacitinib (EAER, 0.9) than with placebo (EAER, 0), all in patients with UC. The EAERs for malignancies excluding non-melanoma skin cancer were as follows: 0.6 in the group that received 15 mg of upadacitinib, 1.0 in the group that received 30 mg of upadacitinib, and 0.4 in the placebo group.

Another post hoc study evaluated outcomes from patients who had a CD activity index (CDAI) of at least 220 at baseline in the phase 3 U-EXCEED and U-EXCEL induction trials

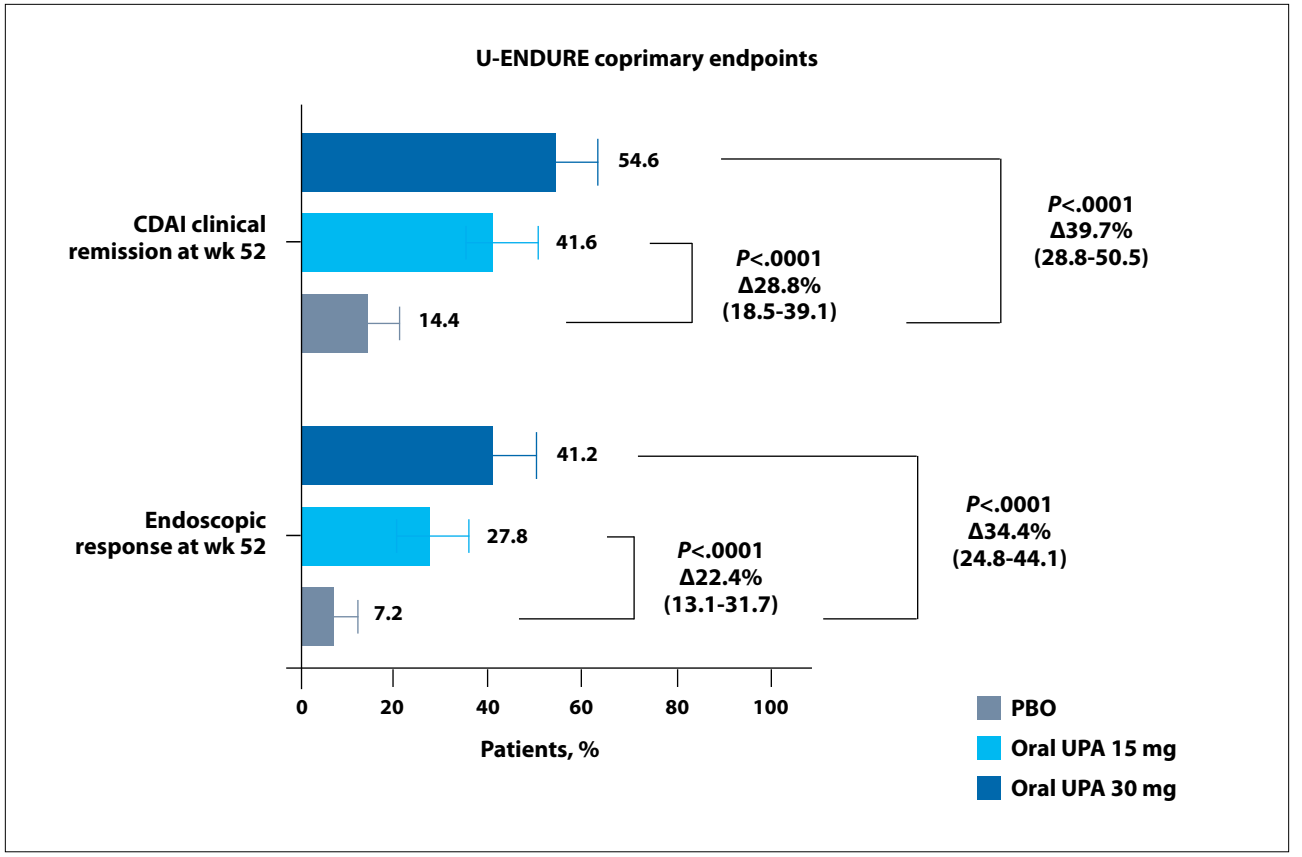

Figure 2. U-ENDURE maintenance results among patients who had CDAI ≥220 at induction BL and achieved CDAI ≥100 at maintenance wk 0.

BL, baseline; CDAI, Crohn's Disease Activity Index; PBO, placebo; UPA, upadacitinib; wk, week.
Adapted from Rubin et al. Abstract P0732. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[6]

(n=857) or who achieved a clinical response (at least a 100-point reduction in the CDAI from baseline [CR-100]) in the phase 3 U-ENDURE maintenance trial of upadacitinib vs placebo (n=343).[6] Among patients with a CDAI of at least 220 at baseline, higher rates of CDAI clinical remission (46.2% vs 22.5% in U-EXCEL; 35.9% vs 17.8% in U-EXCEED; *P*<.0001 for both) and of endoscopic response (45.5% vs 12.6% in U-EXCEL; 34.1% vs 3.4% in U-EXCEED; *P*<.0001 for both) were observed with upadacitinib induction than with placebo (Figure 1). Analysis of key secondary endpoints, including stool frequency/abdominal pain score clinical remission, CR-100, steroid-free clinical remission, and endoscopic remission, also showed significantly superior outcomes with upadacitinib vs placebo in this patient subgroup. No new safety signals emerged.

Patients from U-ENDURE who were included in the analysis had achieved a CR-100 with upadacitinib induction therapy. At week 52 of maintenance therapy, the rates of CDAI clinical remission were 54.6% with upadacitinib (30 mg), 41.6% with upadacitinib (15 mg), and 14.4% with placebo (*P*<.0001), and the rates of endoscopic response were 41.2%, 27.8%, and 7.2%, respectively (*P*<.0001) (Figure 2). A higher proportion of patients treated with upadacitinib than with placebo achieved key secondary endpoints, including corticosteroid-free CDAI clinical remission, endoscopic remission, stool frequency/abdominal pain score clinical remission, and others.

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Safety and Efficacy of Risankizumab in Crohn's Disease: Prospective Real-World Experience and Systematic Literature Review

Risankizumab is a selective inhibitor of interleukin-23 (IL-23) that is approved for the treatment of adults with moderately to severely active CD.[1,2] A prospective study evaluated real-world outcomes in 145 patients with CD who were followed for 12 weeks after the initiation of treatment with risankizumab.[3] Of these patients, 81 were treated for active luminal disease and were included in the efficacy analysis, 45 of whom (56%) had received prior treatment with ustekinumab. In the efficacy cohort of 81 patients, the median age was 44 years (interquartile range [IQR], 35-58 years), and the median duration of disease was 15 years (IQR, 9-27 years). More than half of the patients had ileocolonic disease (53%). The most common disease phenotype was stricturing (44%), followed by perianal (31%) and penetrating (20%). In the efficacy cohort, 48% of the patients had received 3 or more prior advanced therapies, and 60% had a history that included bowel resection. By week 12, 70% of patients achieved clinical remission, with 63% achieving corticosteroid-free clinical remission. Most of the patients who achieved clinical remission did so by week 4. Among the patients who were ustekinumab-naive vs those who were ustekinumab-experienced at baseline, the rates of clinical remission were 78% vs 64% (*P*=.222), and the rates of corticosteroid-free clinical remission were 75% vs 52% (*P*=.041) (Figure 3); however, in multivariate analysis, prior therapy with ustekinumab was not associated with a lower rate of corticosteroid-free clinical remission at week 12.

A systematic review of literature was conducted to evaluate dosing practices and outcomes in patients who had CD treated with risankizumab.[4] The study included 5 papers: 1 cohort study, 1 phase 2 randomized controlled clinical trial, 1 phase 2 open-label extension trial, and 2 phase 3 randomized controlled clinical trials. Risankizumab was administered intravenously at doses of 200, 600, and 1200 mg and was administered subcutaneously at a dose of 180 mg. The rate of clinical remission, based on a CDAI of less than 150, was 37% (15/41 patients) with 200 mg of risankizumab in the phase 2 open-label trial; the rates of clinical remission were higher in the 2 phase 3 trials, in which risankizumab was administered at either 600 or 1200 mg (42% vs 40% and 45% vs 42%, respectively). Rates of endoscopic remission in the phase 2 and phase 3 trials ranged from 19% to 24% with 600 mg of risankizumab and from 20% to 24% with 1200 mg of risankizumab. In the phase 3 trials, rates of AEs ranged from 51% to

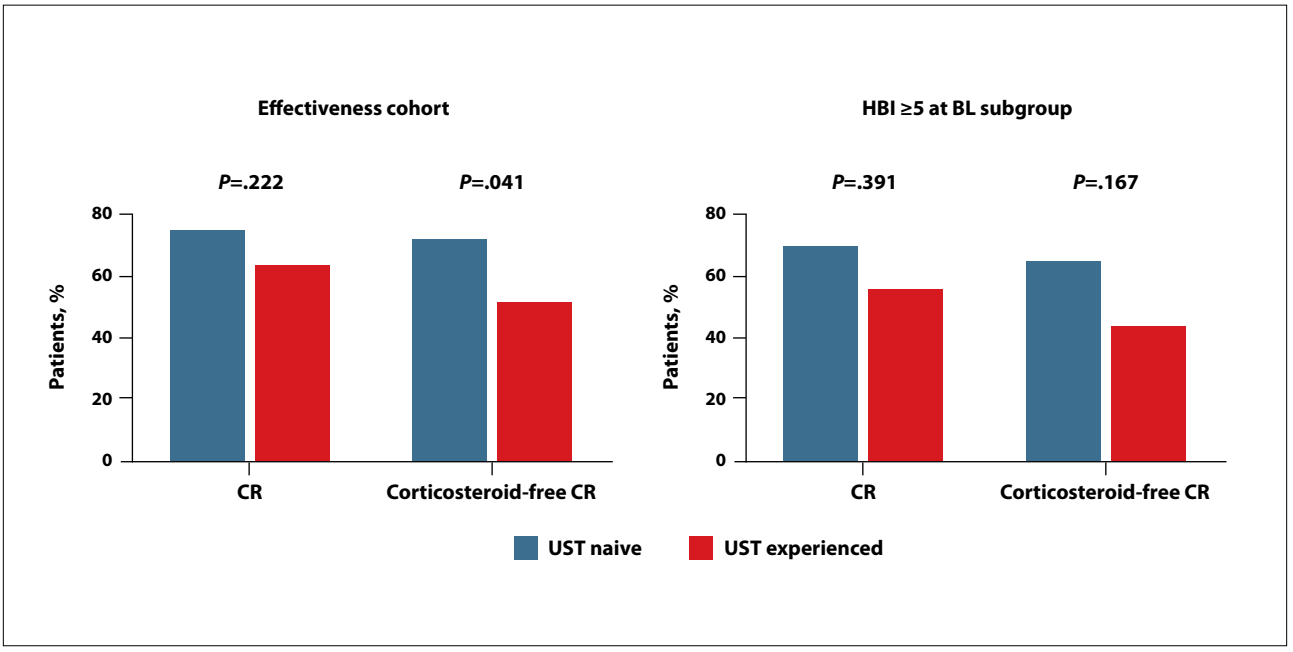

Figure 3. CR and corticosteroid-free CR rates at wk 12 of risankizumab induction therapy in patients with and without prior ustekinumab from the effectiveness cohort and in a subgroup of patients with HBI ≥5 at BL.

BL, baseline; CR, clinical remission; HBI, Harvey-Bradshaw Index; UST, ustekinumab.
Adapted from Zinger et al. Abstract P3532. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[3]

59% with 1200 mg of risankizumab and from 48% to 56% with 600 mg of risankizumab; in the phase 2 open-label trial, 600 mg of risankizumab was associated with a higher rate of AEs (76%). In the real-world GETAID cohort study, 600 mg of risankizumab was associated with a 20% rate of AEs and a 7% rate of serious AEs.

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Ustekinumab Reintroduction: Week 16 Results and Baseline Response Analysis From the POWER Study in Patients With Crohn's Disease

Following successful induction with ustekinumab, a secondary loss of response to ustekinumab maintenance therapy administered every 8 weeks develops in some patients with CD.[1-3] The double-blind, multicenter, phase 3b POWER study evaluated the safety and efficacy of a single intravenous dose of ustekinumab vs continuous maintenance with the subcutaneous administration of ustekinumab in patients who had CD with a secondary loss of response to ustekinumab maintenance therapy.[4] The 36-week study enrolled patients with moderately to severely active CD who initially responded to induction therapy with ustekinumab administered intravenously and who experienced a secondary loss of response to maintenance therapy with ustekinumab (90 mg, every 8 weeks) administered subcutaneously. Loss of response was defined as a CDAI higher than 220 to 450 plus either elevated C-reactive protein (CRP), elevated fecal calprotectin, or endoscopic evidence of active CD. Following randomization, 108 patients in arm 1 received reinduction therapy with intravenous ustekinumab (6 mg/kg) plus a subcutaneous placebo, and 107 patients in arm 2 received an intravenous placebo plus continued maintenance therapy with subcutaneous ustekinumab (90 mg, every 8 weeks).

A post hoc analysis was conducted to evaluate pharmacokinetics, pharmacodynamics, and immunogenicity in patients from the POWER trial.[3] Baseline characteristics were well balanced between the 2 arms. The patients had a

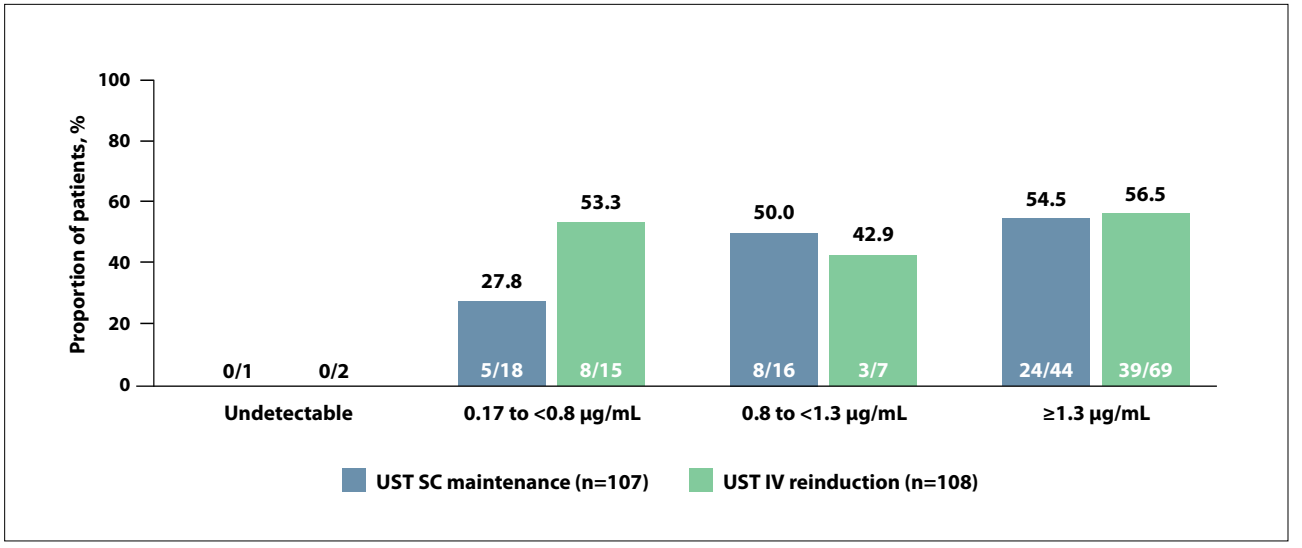

Figure 4. Clinical response[a] at week 16 by ustekinumab trough concentrations at week 16[b] from the POWER trial.

[a]Clinical response: ≥100-point reduction from baseline in CDAI or CDAI <150.
[b]Patients with insufficient data to calculate CDAI, a prohibited CD-related surgery, prohibited concomitant medication changes, or discontinuation of study agent due to lack of efficacy or due to an adverse event indicated to be of worsening CD before the designated analysis timepoint are considered not to be in clinical response.
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IV, intravenous; SC, subcutaneous; UST, ustekinumab.
Adapted from Feagan et al. Abstract 32. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[3]

median age of approximately 41 years and a mean CDAI of 289. Most of the patients (~90%) had previously been exposed to anti-TNF therapy, with or without vedolizumab. Endoscopy in a subset of patients (~60% in each arm) showed relatively mild disease. Most of the patients in each arm (86%-93%) completed treatment at week 16. The serum concentration of ustekinumab reached a median level of 105.62 µg/mL among the patients who received a single intravenous reinduction dose of ustekinumab vs 1.47 µg/mL among the patients who received the intravenous placebo, and it was also higher after intravenous reinduction at week 16. The change in CDAI was evaluated in patients on the basis of the ustekinumab trough concentration at baseline, and the CDAI reduction was superior for ustekinumab reinduction vs intravenous placebo in all groups. At week 16, the proportions of patients in clinical response were similar in the 2 arms among the patients with a trough concentration of ustekinumab at week 16 of at least 1.3 µg/mL (Figure 4). Among the patients with a ustekinumab serum trough concentration of at least 1.3 µg/mL, a greater proportion of those in arm 1 than in arm 2 achieved endoscopic remission (23.8% vs 8.3%). Immunogenicity was not a concern.

A related study investigated baseline characteristics that correlated with a clinical response to reinduction with ustekinumab.[5] Parameters associated with an increased likelihood of achieving a clinical response at week 16 with ustekinumab vs placebo included duration of disease of less than 5 years (*P*=.029), both ileal and colonic involvement (*P*=.002), elevated baseline level of CRP (*P*=.029) or fecal calprotectin (*P*=.045), no more than 1 prior failure with a biologic therapy (*P*=.042), and prior perianal CD-related surgery (*P*=.013).

References

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Efficacy and Safety of Guselkumab in Crohn's Disease: Results From the GALAXI 1 Study

Guselkumab is a selective IL-23 antagonist that binds to p19.[1] The double-blind phase 2 GALAXI 1 study evaluated 3 doses of guselkumab vs ustekinumab or placebo in patients with moderately to severely active CD.[2,3] During the 12-week induction period, patients randomized to the guselkumab arm received 200, 600, or 1200 mg of guselkumab at weeks 0, 4, and 8. For the maintenance and long-term extension (LTE) studies, 100 or 200 mg of guselkumab was administered every 4 or 8 weeks. At week 12 of induction, 34% of the patients treated with guselkumab (63/185) and approximately 33% of those treated with ustekinumab (21/63) had failed to achieve a CDAI response. Compared with the 185 patients who received guselkumab at any dose, those who failed to achieve a response to induction therapy with guselkumab tended to have a longer duration of CD (11.1 vs 9.3 years), and a greater proportion of them had failed treatment with a biologic therapy (60.3% vs 54.6%). By week 48 of maintenance in the subgroup of induction nonresponders, 58.7% of the patients receiving guselkumab and 47.6% of those receiving ustekinumab had achieved a clinical response (Figure 5), and the rate of clinical remission was 41.3% with guselkumab vs 33.3% with ustekinumab. Among the induction nonresponders in the combined guselkumab subgroups vs the ustekinumab subgroup, the rates of remission based on patient-reported outcomes (PROs) were 42.9% vs 23.8%, and the rates of endoscopic response were 31.7% vs 23.8%.

The GALAXI 1 trial included an LTE study to assess clinical, endoscopic, and safety outcomes.[4] The LTE study included 151 patients treated with guselkumab and 48 treated with ustekinumab. Nonresponder imputation was used to account for missing patient data. At week 144, the rate of clinical remission with guselkumab was 95.4% among patients in the LTE observed population and 54.1% in the overall study population; the rate of clinical remission with ustekinumab was 83.8% among patients in the LTE study and 46.0% among all randomized patients. At week 144, rates of endoscopic response were generally maintained with guselkumab (73.5% among observed LTE patients, 34.7% among all randomized patients) and with ustekinumab (41.4% among observed LTE patients, 19.4% among all randomized patients). Rates of endoscopic remission at week 144 with guselkumab were 49.4% in the observed LTE population and 23.3% among all randomized patients; with ustekinumab, the rates were 27.6% in the observed LTE population and

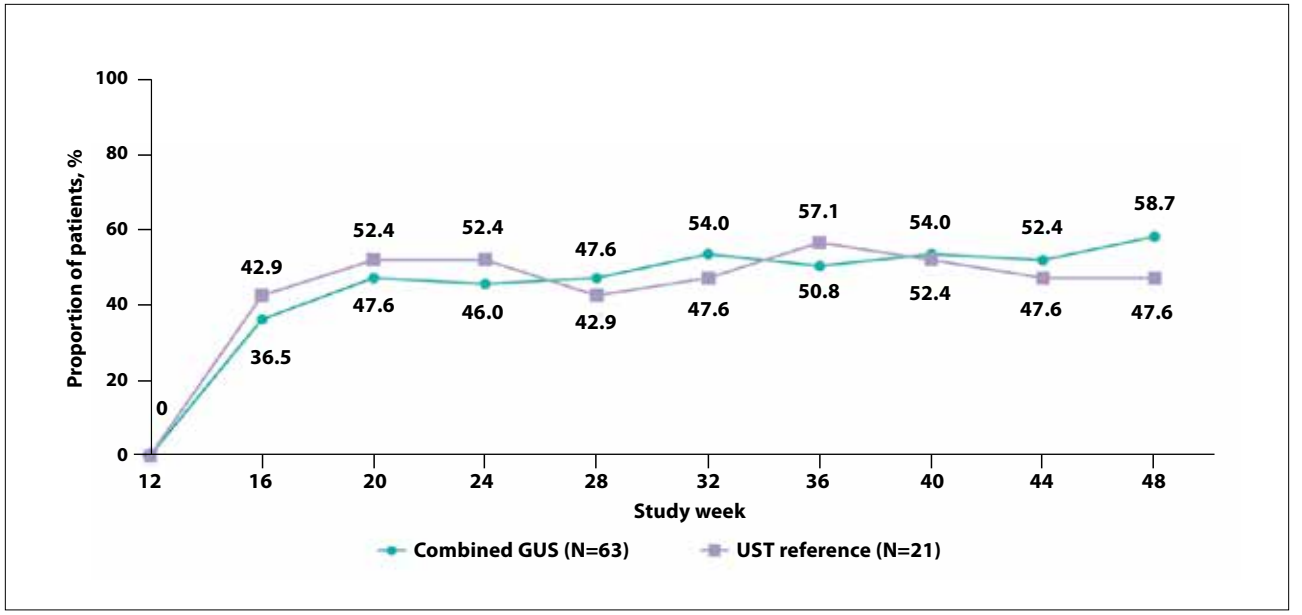

Figure 5. Clinical response[a] among induction nonresponders at week 12 from a post hoc analysis of the GALAXI 1 study.

[a]Clinical response: ≥100-point reduction from BL in CDAI or CDAI <150.
BL, baseline; CDAI, Crohn's Disease Activity Index; GUS, guselkumab; UST, ustekinumab.
Adapted from Panaccione et al. Abstract 69. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[2]

12.9% among all randomized patients. Rates of PRO-2 remission were 89.8% in the observed LTE population and 51.4% among all randomized patients with guselkumab and were 75.7% in the observed LTE population and 39.7% among all randomized patients with ustekinumab. No new safety signals arose. Most infections were not serious; rates of discontinuation, serious AEs, and serious infections were generally low throughout the LTE.

ABSTRACT SUMMARY Comparative Efficacy and Safety of Adalimumab vs Vedolizumab in Managing Moderate-to-Severe Crohn's Disease: A Systematic Review and Meta-analysis

A systematic review and meta-analysis compared safety and efficacy outcomes in patients with CD (Abstract P0764). For the ability to achieve remissions during induction, the analysis showed a significant benefit with adalimumab (odds ratio [OR], 3.037; *P*=.000) or vedolizumab (OR, 2.444; *P*=.000). Similarly, for the induction of response, placebo was inferior to adalimumab (OR, 2.601; *P*=.000) or vedolizumab (OR, 2.254; *P*=.000). In addition, the rate of remissions was lower with placebo maintenance than with adalimumab (OR, 4.808; *P*=.000) or vedolizumab (OR, 2.014; *P*=.000). The rate of serious AEs was significantly higher with adalimumab than with placebo (OR, 0.514; *P*=.000), but the difference in the proportions of serious AEs was not significant in a comparison of vedolizumab vs placebo (OR, 1.284; *P*=.076).

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THE DATA IS IN

See Results From A Head-to-Head Trial

Skyrizi®
risankizumab-rzaa

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

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

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

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

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

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

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

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

PIVOTAL TRIAL STUDY DESIGNS

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

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

INDICATION AND IMPORTANT SAFETY INFORMATION FOR SKYRIZI[1]

INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

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

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

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

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

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

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

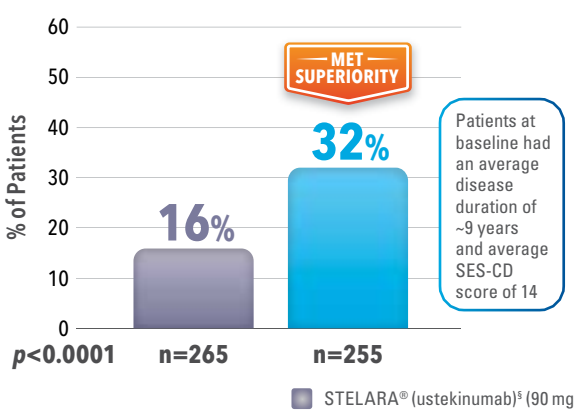
SEQUENCE HEAD-TO-HEAD PRIMARY ENDPOINTS DATA[3,4]

STUDY DESIGN

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

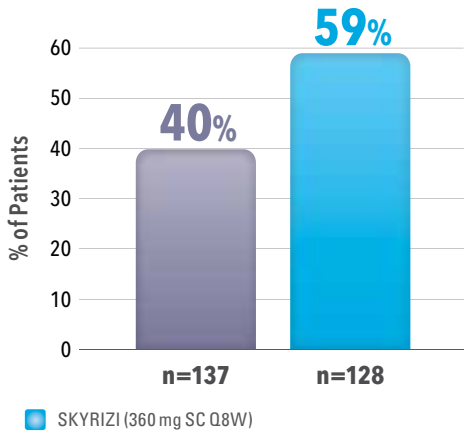
POWERFUL SUPERIORITY DATA[3,4]

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



DEMONSTRATED SYMPTOM RELIEF DATA[3,4]

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



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

SKYRIZI (360 mg SC Q8W)

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

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

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

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

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

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

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

INTERESTED IN SEEING ADDITIONAL RESULTS?
WWW.SKYRIZIHCP.COM

Adverse Reactions

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

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

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

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

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

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

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

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

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

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

abbvie

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

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

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Plaque Psoriasis

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

Psoriatic Arthritis

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

Crohn's Disease

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Infections

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

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

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

Tuberculosis

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

Hepatotoxicity in Treatment of Crohn's Disease

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

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

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

Administration of Vaccines

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Plaque Psoriasis

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

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

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

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

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

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

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

Specific Adverse Drug Reactions

Infections

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

Safety Through Week 52

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

Psoriatic Arthritis

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

Crohn's Disease

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

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

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

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

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

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

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

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

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

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

Specific Adverse Drug Reactions

Infections

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

Lipid Elevations

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

Immunogenicity

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

Plaque Psoriasis

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

Psoriatic Arthritis

By Week 28, approximately 12.1% (79/652) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. None of the subjects who developed antibodies to risankizumab-rzaa had

antibodies that were classified as neutralizing. Antibodies to risankizumab-rzaa were not associated with changes in clinical response for psoriatic arthritis. A higher proportion of subjects with anti-drug antibodies experienced hypersensitivity reactions (6.3% (5/79)) and injection site reactions (2.5% (2/79)) compared to subjects without anti-drug antibodies (3.8% (22/574) with hypersensitivity reactions and 0.7% (4/574) with injection site reactions). None of these hypersensitivity and injection site reactions led to discontinuation of risankizumab-rzaa.

Crohn's Disease

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

Postmarketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

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

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

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

Fetal/Neonatal adverse reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

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

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions

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

Infections

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

Hepatotoxicity in Treatment of Crohn's Disease

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

Administration of Vaccines

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

Administration Instruction

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

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI.

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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AbbVie Inc.
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Real-World Clinical Effectiveness and Safety of Vedolizumab and Ustekinumab in Bio-naive Patients With Complex or Noncomplex Crohn's Disease: Results From the EVOLVE Expansion Study

Real-world outcomes in patients with CD treated with vedolizumab or ustekinumab were evaluated in 2 retrospective, multicenter, observational studies that assessed patient chart data from the EVOLVE Expansion trial.[1-3] The retrospective analyses included patients with either complex or noncomplex CD.[4,5] The Evolve Expansion trial enrolled biologic-naive patients with previously diagnosed CD in whom treatment with ustekinumab or vedolizumab was initiated during the eligibility period in Australia, Belgium, or Switzerland. Complex CD was defined as the presence of 1 or more of the following conditions: active fistula at treatment initiation, any prior CD-related surgery since diagnosis, and any CD-related hospitalization within 12 months before the initiation of treatment. The main study endpoints were clinical outcomes, treatment persistence, and safety. A series of hierarchical algorithms was used to assess clinical outcomes, including clinical response, clinical remission, and mucosal healing.[6]

The patients with complex CD whose data were analyzed included 97 treated with ustekinumab and 99 treated with vedolizumab.[4] After adjustment by inverse probability to treatment weighting, no significant differences in baseline characteristics were found between the 2 treatment cohorts. In the 2 cohorts, the median duration of disease was 9.2 to 9.7 months, and 51% to 52% of the patients had ileal disease without upper tract disease. Disease behavior at baseline was nonstricturing and nonpenetrating in 47% to 49% of patients and was stricturing in 29% to 35% of patients. Most of the patients had moderate disease (68%-70%); severe disease was noted in 16% to 17%. Characteristics of complex CD included fistula before the initiation of treatment (27%-28%), CD-related surgeries since diagnosis (67%-72%), and CD-related hospitalizations in the 12 months before the initiation of treatment (53%).

The analysis generally showed no significant differences between the outcomes of patients with complex CD treated with ustekinumab vs vedolizumab. After 36 months of treatment, the weighted cumulative rate of response was 79.4% with ustekinumab or vedolizumab (*P*=.78), and the weighted cumulative rate of clinical remission was 82.9% to 83.1% (*P*=.58). The rate of weighted cumulative mucosal healing was 78.7% with ustekinumab vs 90.1% with vedolizumab (*P*=.12),

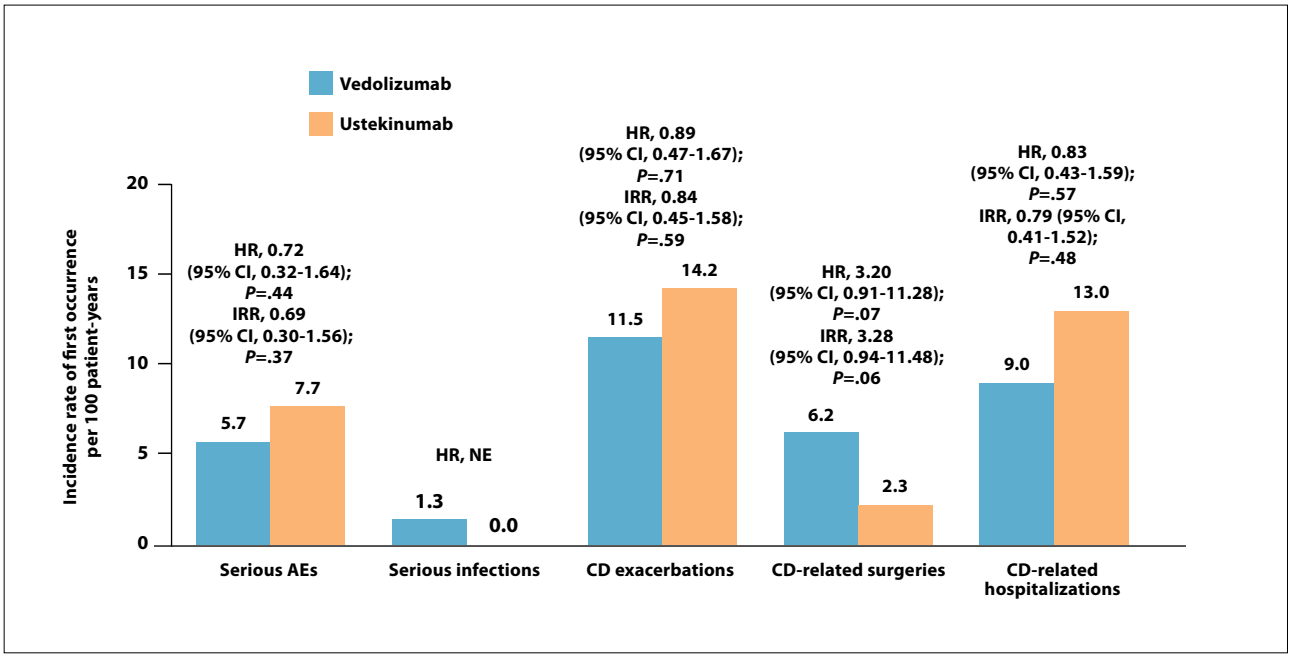

Figure 6. Risk of serious AEs, CD exacerbations, CD-related surgeries, and CD-related hospitalizations in biologic-naive patients with complex CD treated with vedolizumab vs ustekinumab during 36 months of follow-up from the EVOLVE expansion study.

AE, adverse event; CD, Crohn's disease; IRR, incidence rate ratio; HR, hazard ratio; NE, nonestimable.
Adapted from Ferrante et al. Abstract 71. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[4]

and the rate of weighted cumulative treatment persistence was 70.9% with ustekinumab vs 73.9% with vedolizumab (*P*=.83). Similarly, after 12 or 24 months of follow-up, no significant differences in clinical outcomes were observed. During 36 months of follow-up, rates of serious infections were low (incidence rate of first occurrence per 100 patient-years [$IRFO_{100}$], 0.0 with ustekinumab vs 1.3 with vedolizumab; hazard ratio [HR], not estimable). With ustekinumab vs vedolizumab, the $IRFO_{100}$ was 7.7 vs 5.7 for serious AEs (HR, 0.72; 95% CI, 0.32-1.64; *P*=.44), 14.2 vs 11.5 for CD exacerbations (HR, 0.89; 95% CI, 0.47-1.67; *P*=.71), 2.3 vs 6.2 for CD-related surgeries (HR, 3.20; 95% CI, 0.91-11.28; *P*=.07), and 13.0 vs 9.0 for CD-related hospitalizations (HR, 0.83; 95% CI, 0.43-1.59; *P*=.57) (Figure 6).

A related study retrospectively examined real-world data from patients with noncomplex CD in the EVOLVE study.[5] Patients with noncomplex CD were those who did not have active fistula at baseline, had no prior CD-related surgery since diagnosis, and had no CD-related hospitalization before baseline. This study also used the hierarchical algorithms for clinical assessment, and inverse probability of treatment weighting was used to adjust patient data at baseline. The study included 218 patients treated with ustekinumab and 209 treated with vedolizumab. Patient baseline characteristics were similar in the 2 treatment cohorts. Among the patients with noncomplex CD, after 36 months of follow-up, ustekinumab and vedolizumab yielded rates of clinical and safety endpoints that did not differ significantly on the basis of clinical response, clinical remission, mucosal healing, treatment persistence, serious AEs, serious infections, CD exacerbations, CD-related surgeries, and CD-related hospitalizations (*P*>.05 for each).

ABSTRACT SUMMARY Association of Non-switched Memory B-cell (MBC) Levels With Ozanimod (OZA) Efficacy in Patients (Pts) With Moderately to Severely Active Crohn's Disease (CD): Results From the Phase 2 STEPSTONE Study

An exploratory analysis of data from the STEPSTONE study evaluated the association between circulating levels of specific lymphocyte populations and efficacy outcomes after 12 weeks of induction therapy with ozanimod (Abstract P3572). Among 52 patients, the most consistent results were observed for levels of non-switched memory B cells at baseline. Patients with higher vs lower levels of non-switched memory B cells at baseline were more likely to achieve an endoscopic response (*P*=.0046), endoscopic remission (*P*=.0054), remission based on the global Geboes histological score (*P*=.0046), and mucosal healing (*P*=.0039). Reductions in levels of non-switched memory B cells by week 12 were associated with reduced clinical and histologic disease activity.

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Insights on Filgotinib in Crohn's Disease From the DIVERSITY1 and SELECTION Studies

Filgotinib is a JAK inhibitor approved by the European Medicines Agency for the treatment of patients with moderately to severely active UC.[1] The double-blind, phase 3 DIVERSITY1 study investigated filgotinib vs placebo as induction and maintenance therapy in patients with moderately to severely active CD.[2] Patients were evenly randomized to receive 100 or 200 mg of filgotinib daily or placebo for 10 weeks during induction or through week 58 for maintenance therapy. Induction study A included patients with or without prior biologic exposure, and study B included only patients who were biologic-experienced. After the induction period, patients with a response to filgotinib were randomized in a 2:1 ratio to continue with filgotinib at the induction dose or to receive placebo. The study had 2 primary endpoints: clinical remission, defined as a CDAI of less than 150, and endoscopic response, defined as a reduction of at least 50% in the Simple

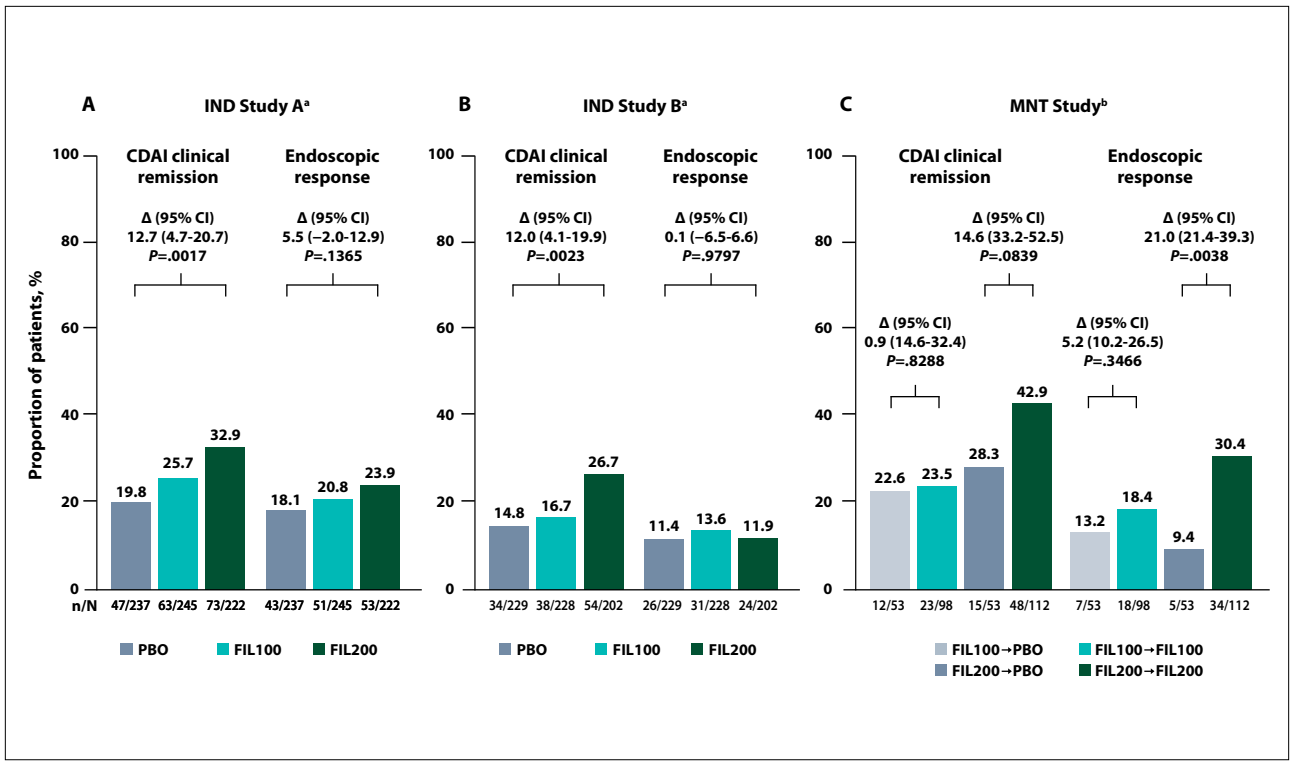

Figure 7. Coprimary endpoints at week 10 of IND study A and IND study B and at week 58 of the MNT study of filgotinib in Crohn's disease from the phase 3 DIVERSITY1 trial.

[a]The FAS for the IND studies included all randomized patients who received ≥1 dose of filgotinib or placebo.
[b]The FAS for the MNT study included all rerandomized responders (endoscopic response or PRO2 clinical remission at week 10) who received ≥1 dose of filgotinib or placebo during the MNT study.
Δ, difference; CDAI, Crohn's Disease Activity Index; FAS, full analysis set; FIL, filgotinib; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; IND, induction; MNT, maintenance; PBO, placebo; PRO2, 2-item patient-reported outcome.
Adapted from Vermeire et al. Abstract P0727. Presented at: ACG 2023; October 20-25, 2023; Vancouver, British Columbia, Canada.[4]

Endoscopic Score for Crohn's Disease (SES-CD) from baseline or clinical remission on the basis of a 2-item PRO.

The DIVERSITY1 study enrolled 1363 patients into 6 arms. After 10 weeks of induction therapy, the rate of clinical remission was significantly higher among the patients treated with 200 mg of filgotinib than among those treated with placebo in study A (32.9% vs 19.8%; *P*=.017) and in study B (26.7% vs 14.8%; *P*=.0023) (Figure 7). However, the rates of endoscopic response were not significantly different for filgotinib vs placebo in either study A or study B (*P*>.05). In the maintenance portion of the study, the only comparison that was significant was the rate of endoscopic response in patients who received 200 mg of filgotinib for both induction and maintenance vs the rate in patients who initially received the higher dose of filgotinib and were then randomized to placebo for maintenance (30.4% vs 9.4%; *P*=.0038).

The international phase 2b/3 SELECTION study compared filgotinib at 100 or 200 mg daily vs placebo in 1348 patients with moderately to severely active UC.[3] In a safety analysis, patient data from the 2 studies were used to compare filgotinib toxicity in patients with UC vs toxicity in patients with CD.[4] Filgotinib was generally well tolerated, with no new safety signals arising. Rates of specific AEs, such as serious infections, malignancies excluding nonmelanoma skin cancer, venous thromboembolism, and major adverse cardiovascular events, were similar among patients with CD and those with UC. A gastrointestinal perforation developed in 11 of the patients with CD, but none was considered related to filgotinib therapy. No deaths occurred that were considered related to study treatment.

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Highlights in Crohn's Disease From the American College of Gastroenterology (ACG) 2023 Annual Scientific Meeting: Commentary

David T. Rubin, MD
Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology, and Nutrition
Director, Inflammatory Bowel Disease Center
The University of Chicago Medicine
Chicago, Illinois

The American College of Gastroenterology (ACG) 2023 Annual Scientific Meeting, which was held in Vancouver, Canada, this October, provided valuable insights into the management of Crohn's disease (CD). Data focused on the efficacy, safety, and utilization of treatment options among several single-agent therapies, including upadacitinib, filgotinib, risankizumab, guselkumab, ustekinumab, and vedolizumab.

Upadacitinib

Upadacitinib is a synthetic small-molecule therapy that targets the Janus kinase (JAK) mechanism of inflammation. JAK is a transmembrane enzyme that activates inflammatory pathways, and upadacitinib inhibits primarily JAK1.[1,2] In a study analyzing the safety of upadacitinib in an inflammatory bowel disease (IBD) pooled analysis of phase 3 maintenance studies, Panaccione and co-investigators reviewed trials in both CD and ulcerative colitis (UC) to explore the safety profile of this therapy for patients with these disorders.[3] The study included 2 phase 3 double-blind placebo control trials and more than 1400 patients, with 246.4 patient-years of exposure to placebo, 353.1 patient-years of exposure to upadacitinib at 15-mg dosing, and 395.7 patient-years of exposure to upadacitinib at 30-mg dosing. Notably, the frequencies of serious adverse events (AEs), events leading to treatment discontinuation, and serious infections were similar with the 2 doses of upadacitinib (15 and 30 mg) and lower than those observed in the placebo group. This trend is often seen in trials of moderate to severe CD, in which patients receiving a placebo during maintenance phases tend to experience disease relapse or progression because of the lack of treatment. The adjudicated AEs did not show any cardiovascular events, nor were any significant venous thromboembolic (VTE) events noted among a cohort of patients who had severe IBD and would otherwise have had a higher risk for VTE. This analysis is of specific interest because the drug class labeling advises screening and risk assessment for thromboembolic complications, on the basis of prior studies in a high-risk cohort of patients with rheumatoid arthritis who were treated with tofacitinib.[4] Overall, this analysis was helpful. It showed the benefit of the treatment in patients with moderate to severe CD and moderate to severe UC from a safety point of view. Also, it provided reassurance by not showing any additional safety signals associated with this specific therapy.

The second study of interest, which I had the honor of leading, focused on the efficacy of upadacitinib in patients with CD; the Crohn's Disease Activity Index (CDAI) was used as a measure of efficacy.[5] This study

ABSTRACT SUMMARY Efficacy and Safety of Mirikizumab in Patients With Crohn's Disease: 104-Week Extension Results From a Phase 2 Randomized Controlled Trial

The SERENITY trial investigated the safety and efficacy of 3 dose levels of mirikizumab vs placebo in patients with moderately to severely active CD (Abstract P2109). During the extension study (weeks 53-104), patients received mirikizumab either intravenously or subcutaneously. Among the patients who showed endoscopic improvement after 12 weeks of induction therapy, rates of CDAI remission and PRO remission were maintained from week 52 through week 104. At week 104, the rate of CDAI remission was 66.7% with intravenous mirikizumab and was 61.0% with subcutaneous mirikizumab; the rate of PRO remission was 63.6% with intravenous mirikizumab vs 46.3% with subcutaneous mirikizumab. No unexpected AEs were observed.

holds relevance because of the difference in requirements between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in assessing therapeutic efficacy for CD. In Europe, new therapies are evaluated with patient-reported outcomes of stool frequency and abdominal pain scores, without utilization of the CDAI, whereas in the United States, the FDA has continued to use the CDAI. The reanalysis of the efficacy of upadacitinib in moderate to severe CD with the CDAI was performed to evaluate whether this therapy had a similar benefit when that index was used. The post hoc analysis included 857 patients with a baseline CDAI of 220 points or more. The patients received 12 weeks of a 45-mg induction dose of upadacitinib or placebo. In all, 343 patients from the maintenance trial achieved a clinical response of a 100-point improvement in the CDAI at the 45-mg dose. They were then rerandomized to a maintenance dose of either 15 or 30 mg of upadacitinib or to placebo. The bottom line here for clinicians is to understand that when this other measure of response and remission and inclusion criteria were used, the efficacy of upadacitinib was similar to what had been described when the patient-reported outcomes were used alone. This finding reaffirms our current understanding and does not alter our perspective on this treatment approach.

Another noteworthy abstract involving upadacitinib, presented at the ACG meeting by Krugliak Cleveland, explored the utility of point-of-care intestinal ultrasonography (IUS) as a way to assess response to therapy and adjust treatments.[6] The study was based on the hypothesis that if a clinician knows that disease is active or not responding to therapy as expected, the therapy can be adjusted sooner than can be done while waiting for the results of standard tests, such as colonoscopy and stool markers, or waiting for complications to arise. The study reviewed 30 of 105 patients receiving upadacitinib at our center, and these patients were stratified into groups; 11 received management guided by IUS, and 19 matched controls underwent conventional management without IUS. Among those patients who had access and were monitored with IUS, therapy was adjusted and remission was achieved statistically sooner than among those managed conventionally. This finding demonstrates the spreading wave of knowledge and excitement about IUS, both in the United States and globally, as point-of-care testing facilitates real-time decision making and therapy adjustments.

Filgotinib

Filgotinib is a different synthetic small molecule that selectively targets JAK1. Vermeire and colleagues presented the phase 3 DIVERSITY1 study, which looked at the efficacy and safety of filgotinib as a treatment for moderate to severe CD.[7] The study compared 2 different doses (200 and 100 mg) with a placebo during a 10-week induction, followed by a subsequent maintenance study extending to week 58. In the maintenance study, patients responding to filgotinib were randomized in a 2:1 ratio to their specific induction dose or to placebo if they had an endoscopic response or a clinical remission. The disappointing result was that filgotinib at 200 mg was not superior to placebo in regard to both coprimary endpoints during the induction phase. However, it did prove efficacious in inducing CDAI clinical remission by week 10. Among patients achieving either endoscopic response or clinical remission in terms of abdominal pain and stool frequency by week 10, filgotinib at 200 mg demonstrated efficacy in sustaining endoscopic response until week 58 in the maintenance trial. Despite these positive aspects, because the therapy failed to meet its primary endpoints, it will not be considered an option for patients with CD. If you look at the trial results, a notable observation is the relatively high placebo rate during induction, which may have been due to concomitant therapies, including corticosteroids.

Schreiber and colleagues also assessed the safety of filgotinib by looking at data from various trials, including DIVERSITY1 in CD and SELECTION in UC.[8] Given the availability of other JAK inhibitors to treat IBD and the efficacy of filgotinib in treating moderate to severe UC in Europe and other regions, it is worth noting that the safety profile of filgotinib

ABSTRACT SUMMARY Efficacy and Safety of Omilancor in a Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of Patients With Crohn's Disease

A double-blind, parallel-group, phase 2 proof-of-concept study investigated 12 weeks of omilancor (n=12) vs placebo (n=11) in patients with moderately to severely active CD (Abstract P2215). The study demonstrated a superior rate of clinical remission with omilancor vs placebo (25.0% vs 9.1%; Δ=15.9%). Similar differences in clinical remission rates were observed with omilancor vs placebo in patients who had prior exposure to biologic therapy (Δ=20.0%) and patients who were biologic-naive (Δ=14.3%). The rates of clinical response and PRO-2 remission were also superior with omilancor (Δ=32.6% for both). Normalization of the fecal calprotectin level was reported in 33.3% of patients treated with omilancor vs 14.3% of those treated with placebo (Δ=19.0%). Omilancor was generally well tolerated, with no serious AEs that were considered related to study therapy.

as a JAK inhibitor is similar to what has been observed with tofacitinib and upadacitinib, showing no new so safety signals. Infections were reported in approximately 25% to 34% of patients with CD and in 23% to 34% of patients with UC, with the rate of serious infections remaining below 2% in both populations. Malignancy occurred only in 1 patient with CD and 1 patient with UC. In the maintenance studies, 1 patient with CD and 1 patient with UC experienced a VTE event; similarly rare occurrences of major adverse cardiovascular events were noted, without any additional concerns raised. Importantly, no deaths occurred in the DIVERSITY1 trial. In the SELECTION trial, 2 deaths occurred, but neither was related to the drug as reported by the investigator and adjudicated by the steering committee.[9] Overall, the safety assessment for filgotinib provides us with valuable information about the particular mechanism in patients with CD and UC, offering reassurance in terms of safety. However, it is disappointing that filgotinib will not be considered an option to treat patients with moderate to severe CD. Of note, it is not available for UC in the United States.

ABSTRACT SUMMARY The Anti-TL1A Antibody PRA023 Demonstrated Proof of Concept in Crohn's Disease: Results of the Phase 2a APOLLO-CD Study

The open-label, multicenter, phase 2a APOLLO-CD study investigated the safety and efficacy of MK-7420 [PRA023] as induction therapy in patients with moderately to severely active CD (Abstract P3581). Among 53 patients who completed 12 weeks of induction monotherapy, the rate of endoscopic response was 26% and was significantly better than the rate with a historical placebo control (12%; *P*=.002). The rate of clinical remission was also superior with MK-7420 vs the historical placebo control (49% vs 16%; *P*<.001). Among patients with prior exposure to biologic therapy, the rate of endoscopic response was 33% and the rate of clinical remission was 39%. Efficacy was not affected by the concurrent use of steroids or immunosuppressants. No serious or severe AEs were considered related to the study therapy.

Ustekinumab

Ustekinumab, a monoclonal antibody that targets the protein p40, effectively inhibiting both interleukin 12 (IL-12) and IL-23, is available as a treatment for moderate to severe CD and moderate to severe UC. The highly anticipated additional results of the POWER study, initially introduced earlier in the year, were presented at ACG.[10] This study compared the efficacy and safety of an additional intravenous (IV) dose of ustekinumab for reinduction vs subcutaneous dosing in patients who had lost response to standard ustekinumab maintenance therapy. Loss of response to various therapies in CD is well described and unfortunately remains a challenge in managing this condition. Therefore, understanding the potential to optimize existing therapies before transitioning to other treatments is of great interest. The hypothesis here is based on the presumption that subtherapeutic levels of the drug may be affecting change in patients, leading to a loss of response. The thought was to investigate whether providing an additional IV dose could boost efficacy and recapture and redirect the patient's response. At ACG, Feagan and colleagues presented updated results of the POWER study, also delving into the details inherent to the hypothesis and the study design, such as how the pharmacokinetics, exposure-response relationships, and the potential for immunogenicity affect how the drug works.[11] In the study, patients who had initially responded to induction with IV ustekinumab but later lost response were identified either by a rising CDAI score plus elevated C-reactive protein and fecal calprotectin levels or with endoscopy. This dual assessment ensured confirmation of a biological relapse, differentiating it from a merely symptomatic relapse. When a patient's loss of response is assessed, it is important to distinguish between symptoms caused by active disease and those unrelated, always seeking objective measures to comprehend the situation, and also, naturally, to exclude infection. The bottom line from this complex analysis revealed that among 2015 patients with ustekinumab concentration data and one or more collected blood samples, on the basis of week 16 trough concentrations, no substantial difference was observed between those who were successfully recaptured and those who were not. However, patients did show increased trough levels with the IV dose vs continuation of the subcutaneous dose, which would have been expected. Although higher drug levels were observed, no significant difference in the clinical response was noted between the IV and the subcutaneous strategies. In a quartile analysis, a relationship was noted between increased exposure in the IV arm and differences in endoscopic remission, but not in the clinical response. The takeaway message for this study is that IV reinduction does not offer much clinical benefit and therefore would not be routinely recommended.

Risankizumab

Risankizumab, which has received approval for treating moderate to severe CD, belongs to the new generation of IL-23 inhibitors. The drug operates as a monoclonal antibody;

targeting the protein p19, it is selective for IL-23 and does not affect IL-12.[12] This particular study, presented by Zinger and colleagues at ACG, focuses on the real-world experience when this therapy was used at the University of Chicago and reports induction data outcomes.[13] The study involved a prospective analysis of clinical outcomes in patients with CD who received risankizumab. Clinical evaluations were performed at weeks 0, 2, 4, 8, and 12 with the Harvey Bradshaw Index (HBI). In all, 94 patients underwent ongoing follow-up for 12 weeks. After a rapid onset of action of risankizumab, with a median HBI reduction as early as 2 weeks, a plateau was reached by week 8, even before the 12-week endpoint. By week 12, 78% of the patients had achieved a clinical response, and 70% achieved clinical remission. Of great interest in this particular study was that most patients had previously received ustekinumab. Interestingly, when patients who had received ustekinumab were compared with those who were ustekinumab-naive, no statistical difference was seen in the likelihood of response. Given the similarity in the mechanisms of action of these 2 therapies, this finding is particularly noteworthy. Notably, the rate of corticosteroid-free clinical remission was higher in ustekinumab-naive patients than in those who were ustekinumab-experienced. Overall, the safety profile aligned with what has been observed in this class of therapy, demonstrating excellent safety. This real-world experience closely mirrors or even slightly surpasses what has been seen in clinical trials and gives us further insight into the utility of this therapy, even in patients previously treated with ustekinumab.

Guselkumab

Guselkumab, another p19 monoclonal antibody that selectively targets IL-23, has been studied in both UC and CD.[14] At ACG, Panaccione and colleagues reported updates from the GALAXI 1 study, assessing patients with moderate to severe CD who had not achieved a clinical response at week 12 with guselkumab.[15] Of the patients who received guselkumab at various doses, those who did not achieve a response were allowed to continue therapy. This post hoc analysis evaluated the patients who continued treatment. By week 24, 46% of the nonresponders had achieved a clinical response. Among those who were in the maintenance study up to week 48, 58.7% achieved clinical response and 47.6% achieved clinical remission. The concept of delayed response has been well documented with other therapies and is a standard approach in these trials, in which the study design of randomizing responders or focusing on post-induction responders and their maintenance outcomes is of particular interest. The secondary analysis that is often performed explores the outcomes of patients who took longer to respond but eventually did. Repeatedly, we have learned that this group of patients, even if they experience moderate improvement without achieving remission or a defined significant response by the trial endpoint, are likely to respond positively if treatment is continued for an additional induction period—in this case, 12 weeks. Those who do eventually respond are equally likely to do well during maintenance. The interpretation of this study suggests that it is beneficial for some patients to continue the therapy beyond week 12 to assess whether control of their CD can be achieved.

The other study of guselkumab, presented by Afzali and colleagues, reported 3-year outcomes in patients from the GALAXI 1 long-term extension.[16] The average duration of follow-up in this analysis from baseline through week 152 was more than 100 weeks in the guselkumab group and 102 weeks in the ustekinumab comparator group. Overall, the 151 patients who were randomized to guselkumab and the 48 patients who were randomized to ustekinumab were treated in the long-term extension. The primary results demonstrated that patients continue to do well, with 54% in CDAI clinical remission and 34% in endoscopic response at week 144. In terms of safety, the mechanism of this particular drug is quite safe. Most infections were not serious and were mild to moderate, resolving without a requirement for drug discontinuation. As we have seen repeatedly with the IL-23 mechanism, no cases of active tuberculosis, opportunistic infections,

ABSTRACT SUMMARY Real-World Clinical Effectiveness and Safety of Vedolizumab and Ustekinumab in Bio-naïve Patients With Early Crohn's Disease: Results From the EVOLVE Expansion Study

A post hoc analysis based on 36 months of follow-up evaluated safety and efficacy outcomes in patients from the EVOLVE clinical trial who received vedolizumab or ustekinumab during the study as their biologic therapy (Abstract P0685). The analysis showed similar outcomes with vedolizumab vs ustekinumab in terms of cumulative rates of clinical response (81.6% vs 80.7%; *P*=.31), clinical remission (87.9% vs 85.0%; *P*=.74), and treatment (64.9% vs 78.1%; *P*=.49). However, the rate of mucosal healing was superior with vedolizumab (92.3% vs 89.0%; *P*=.03). Safety outcomes were also similar for the 2 biologic therapies in regard to serious AEs (*P*=.79), serious infections (*P*=.14), CD exacerbations (*P*=.91), CD-related surgeries (*P*=.18), and CD-related hospitalizations (*P*=.97).

anaphylaxis or serum sickness, major adverse cardiovascular events, or deaths occurred.

Ustekinumab and Vedolizumab

The EVOLVE expansion study is a multicenter, real-world, retrospective analysis of patients with CD treated with ustekinumab or vedolizumab in Australia, Belgium, and Switzerland from 2016 to 2021. Ferrante and colleagues presented 2 different abstracts at ACG on the relative efficacy and safety of these therapies in patients with complex or noncomplex CD.[17,18] The first abstract explored patients with noncomplex CD who were bio-naive and treated with vedolizumab, an anti-integrin therapy that targets the integrins related to lymphocyte trafficking in the gut, or with ustekinumab.[17] Among the patients with noncomplex CD, the 2 therapies were similar in efficacy and the safety was excellent, with no significant differences. We have come to appreciate that both mechanisms are safe, and it is helpful to know that the therapies work well, especially in bio-naive patients. In general, when you treat patients with CD earlier, they are more likely to do well, and according to this retrospective multicenter analysis, they are equally likely to do so regardless of which therapy is used.

In the patients who had complex CD—which is of great interest because of the prevalence of complex disease presentations involving draining fistulas, hospitalization, or surgery—rates of efficacy and safety for ustekinumab and vedolizumab were also similar.[18] CD exacerbations were reduced with both therapies, with a hazard ratio of 0.89. The rates of CD-related surgeries did not differ with the 2 drugs, and CD-related hospitalizations appeared to be reduced during the 36 months of review. The takeaway for clinicians is that both therapies exhibit efficacy and can be utilized in patients with complex presentations. My message would be to ensure that regardless of the chosen treatment, think carefully about measuring that it is actually doing what you need it to do. Remember too that these therapies have different mechanisms and may not work as well for patients with a variety of extraintestinal manifestations.

Relevant Disclosures

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