Clinical Perspectives in IBD: An IL-23 Inhibitor with Head-to-Head Results in an Open-Label Crohn's Disease Study.

Sponsored by AbbVie Medical Affairs

Chapter	Transcript
Chapter 1: An IL-23 Inhibitor's Phase 3 Clinical Trial Program	Hello, my name is Dr. Dulai and I'm an associate professor of medicine at Northwestern University's Feinberg School of Medicine. I specialize in gastroenterology and hepatology. Interleukin 23 signaling is an important inflammatory driver of Crohn's disease pathogenesis. Risankizumab is an interleukin 23 inhibitor indicated for the treatment of moderately to severely active Crohn's disease in adults. Here, we'll delve into risankizumab's Phase 3 data and Crohn's disease and discuss the implications for our patients. The Phase 3 program consisted of two induction studies, ADVANCE and MOTIVATE. ADVANCE included patients who had failed conventional or biological therapy, while MOTIVATE included only patients who had failed biologic therapy. Patients received either 600 mg or 1200 mg of risankizumab or placebo. Please note that 600 mg of risankizumab is the approved dose for induction, but 1200 mg is not. The co-primary endpoints were clinical remission and endoscopic response at Week 12. Patients who responded to intravenous risankizumab induction could transition to the 52-week maintenance trial, FORTIFY. Patients in FORTIFY were randomized to receive one of three treatments, subcutaneous risankizumab every eight weeks at 360 or 180 mg or withdraw to placebo. The co-primary endpoints of the maintenance study were clinical remission and endoscopic response at Week 52. We will focus on the 600 mg dose for ADVANCE and MOTIVATE as this is the US Food and Drug Administration approved induction dose. Both 360 mg and 180 mg doses are US FDA approved for maintenance. Overall, the induction populations were representative of a patient population with moderate-to-severe Crohn's disease. The patients in these trials generally reflect my own patients who come to me with moderate to severe Crohn's disease. Typically, they have been living with Crohn's disease for about a decade, most have some prior exposure to a biologic and their disease scores indicate moderate-to-severe disease activity. These are the first studies to evaluate both clinical and endoscopic outcomes for co-primary endpoints.

See Important Safety Considerations on pages 5-6.

RISN-US-00049-MC Approval date: January 2025 V1.0

	At the end of the induction periods in both studies, a significantly greater proportion of patients in the risankizumab arm achieved the co-primary endpoints. In ADVANCE, 45% of patients treated with risankizumab achieved clinical remission versus 25% on placebo, and 40% of risankizumab-treated patients achieved endoscopic response versus 12% of placebo. Significantly higher percentages of patients treated with risankizumab achieved secondary endpoints of clinical response and endoscopic remission compared to placebo. We see a similar picture when looking at the maintenance study. At Week 52, significantly higher percentages of patients achieved the co-primary endpoints of clinical remission and endoscopic response with both risankizumab doses versus the withdrawal to placebo. 61 and 57% of patients treated with 180 and 360 mg, respectively, of risankizumab achieved clinical remission versus 46% of those on placebo, and 50 and 48% of those on 180 and 360 mg of risankizumab achieved endoscopic response versus 22% on placebo. And for the secondary endpoints of clinical response and endoscopic remission, responses for both doses were numerically higher than placebo. However, these endpoints fell below the hierarchical testing procedure for statistical significance. The higher rates of clinical remission and clinical response seen in patients withdrawn to placebo may be attributed to pharmacokinetic factors. These patients have previously received and responded to 12 weeks of risankizumab in induction. Given the long half-life of risankizumab is 21 days, patients would have had the drug on board for over 100 days.
Chapter 2: Overview of SEQUENCE, An Open-Label, Head-to-Head Trial Design in Crohn's Disease	Let's move on to discuss the Phase 3b head-to-head clinical trial. This trial used endpoint testing for non-inferiority and superiority. Non-inferiority trials aim to show that one treatment is at least as effective as the comparator drug to provide an alternative option for care. Superiority trials aim to show that one treatment is better than an active comparator to potentially establish new treatment protocols. Now let's look at some new data for risankizumab against an active comparator, ustekinumab. SEQUENCE was an open-label, Phase 3b, randomized, efficacy assessor-blinded study that enrolled adult patients with moderate-to-severe Crohn's disease who had intolerance or an adequate response to at least one TNF inhibitor. Risankizumab and ustekinumab are both used in patients with moderate-to-severe Crohn's disease, so a head-to-head comparison can be useful in making decisions with clinical and endoscopic improvement in mind. Ustekinumab blocks activation of interleukin 12 and 23 receptors and this inhibits downstream signaling of T helper 17 and T helper 1 cell

See Important Safety Considerations on pages 5-6.

	pathways. Risankizumab blocks activation of the interleukin 23 receptor which inhibits the downstream T helper 17 pathway. SEQUENCE randomized 520 patients to receive either a single intravenous infusion of ustekinumab at baseline and subcutaneous injections at every eight weeks thereafter or three intravenous infusions of risankizumab at baseline, Week 4 and Week 8 with subcutaneous injections every eight weeks thereafter for up to 48 weeks. The percentage of patients achieving clinical remission at Week 24 was a primary non-inferiority endpoint and the percentage of patients achieving endoscopic remission at Week 48 was a primary superiority endpoint of risankizumab to ustekinumab. Some things to keep in mind as we go through this trial are that the open label nature of the study may have influenced the results and the comparative effectiveness of risankizumab 180 mg which is unknown as it was not evaluated in this study. You should use the lowest effective dose of risankizumab to maintain response in your patients.
Chapter 3: SEQUENCE: Head-to-Head Data from an Open-Label Crohn's Disease Study	Patient demographics were generally balanced across treatment arms. Mean age was 38 years and disease duration at baseline was 9.4 years. Roughly 3/4 of patients had failed one tumor necrosis factor inhibitor, and about 1/4 of patients had failed more than one. Disease severity was reflective of a moderate to severe patient population and was similar between treatment groups except for higher fecal calprotectin in the ustekinumab arm. The primary endpoint was Crohn's disease activity index clinical remission at 24 weeks with a margin of non-inferiority at 10%. Here, we can see the response in risankizumab arm was 19% higher than that in the ustekinumab arm with 58.6% of patients achieving clinical remission versus 39.5% at 24 weeks. At 48 weeks, risankizumab was superior to ustekinumab in achieving clinical remission. A significantly greater proportion of patients were in clinical remission in the risankizumab arm at 60.8% versus 40.8% with ustekinumab. Risankizumab was also superior to ustekinumab in achieving endoscopic remission at week 48, at which point 31.8% of patients treated with risankizumab achieved endoscopic remission versus 16.2% in the ustekinumab arm. Endoscopic response at 24 and 48 weeks was a ranked endpoint for superiority and again, we see that risankizumab was superior to ustekinumab at 24 weeks and these results were stable at 48 weeks. At 24 and 48 weeks, 45.2% and 45.1% of patients in the risankizumab arm

See Important Safety Considerations on pages 5-6.

	had an endoscopic response versus 26.4% and 21.9% of the ustekinumab-treated patients.
Chapter 4: The Safety Data of an IL-23 Inhibitor in Crohn's Disease	Safety was also assessed in the FORTIFY and SEQUENCE trials. The safety profile of risankizumab in Crohn's disease was consistent with the known safety profile of risankizumab. Data was generally consistent with the published safety profiles for both risankizumab and ustekinumab. In FORTIFY, the incidence of infections, serious infections, opportunistic infections, injection site reactions, and hepatic events were higher in the 360 mg dose of subcutaneous risankizumab compared to the 180 mg dose and the group withdrawn to placebo. Keep in mind that risankizumab may increase the risk of infections and you should instruct patients to seek medical advice if they experience signs and symptoms of clinically important infections. If such infections develop, discontinue treatment until the infection has resolved and you should always evaluate patients for TB prior to starting risankiuzmab. Drug induced liver injury during induction has been reported and you should monitor liver enzymes and bilirubin at baseline, during induction and up to 12 weeks of treatment. Then monitor according to routine practice management. Interrupt treatment if drug induced liver injury is suspected until this diagnosis is excluded. The most common adverse events in FORTIFY that occurred in greater than 3% of the study population and higher than in the withdrawal arm were arthralgia, abdominal pain, injection site reactions, anemia, pyrexia, back pain, arthropathy, and urinary tract infections. In SEQUENCE, the most common adverse events included COVID-19, headache and worsening Crohn's disease for the risankizumab group and COVID-19, worsening Crohn's and arthralgia for the ustekinumab group. Overall, no new safety risks were observed for risankizumab and these data reinforces safety profile observed in previous studies. Safety and tolerability of a drug is a big part of the discussion I have with my patients when we decide on treatments. Before initiating treatment, I discuss hypersensitivity reactions, other drugs they might be taking, vaccinations, and I may monitor their alanine and aspartate aminotransferase levels. It's important to have these discussions and plan on how to mitigate risk with a monitoring strategy. The data from these clinical trials give me confidence that Risankizumab can be a safe and effective treatment option in my adult patients with moderate to severe Crohn's disease. Thank you for taking the time to

See Important Safety Considerations on pages 5-6.

	watch today. Next, we'll cover important safety considerations for risankizumab. **IMPORTANT SAFETY CONSIDERATIONS** Risankizumab is contraindicated in patients with a history of serious hypersensitivity reaction to Risankizumab or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis may occur. If a serious hypersensitivity reaction occurs, discontinue Risankizumab and initiate appropriate therapy immediately. Risankizumab may increase the risk of infections. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, discontinue risankizumab until the infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with risankizumab. Drug induced liver injury/hepatotoxicity during induction treatment of Crohn's disease has been reported. Monitor liver enzymes and bilirubin at baseline and during induction (12 weeks). Monitor thereafter according to routine patient management. Consider other treatment options in patients with evidence of liver cirrhosis. Interrupt treatment if drug induced liver injury is suspected until this diagnosis is excluded. Avoid use of live vaccines in patients treated with risankizumab. The most common adverse reactions, greater than 3%, reported during treatment for Crohn's disease are upper respiratory infections, headache and arthralgia during induction dosing, and arthralgia, abdominal pain, injection site reactions, anemia, pyrexia, back pain, arthropathy, and urinary tract infection during maintenance dosing. Review risankizumab-rzaa full prescribing information. For additional information, visit www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110.
Risankizumab Indications and Important Safety Considerations	**INDICATIONS** Risankizumab is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults. Risankizumab is indicated for the treatment of moderately to severely active Crohn’s disease (CD) in adults. **IMPORTANT SAFETY CONSIDERATIONS** Risankizumab is contraindicated in patients with a history of **serious hypersensitivity reaction** to risankizumab or any of the excipients. Serious hypersensitivity reactions, including anaphylaxis, may occur. If a serious hypersensitivity reaction occurs, discontinue risankizumab and initiate appropriate therapy immediately. Risankizumab may increase the risk of **infections**. Instruct patients to seek medical advice

See Important Safety Considerations on pages 5-6.

RISN-US-00049-MC Approval date: January 2025 V1.0

	if signs or symptoms of clinically important infection occur. If such an infection develops, discontinue risankizumab until the infection resolves. Evaluate patients for **tuberculosis** infection prior to initiating treatment with risankizumab. There is a potential for drug-induced **liver injury/hepatotoxicity** during induction treatment of UC and CD. Monitor liver enzymes and bilirubin at baseline and during induction (12 weeks). Monitor thereafter according to routine patient management. Consider other treatment options in patients with evidence of liver cirrhosis. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Avoid use of **live vaccines** in patients treated with risankizumab. The **most common adverse reactions (≥3%) reported during treatment of UC** are arthralgia during induction dosing and arthralgia, pyrexia, injection site reactions, and rash during maintenance dosing. The **most common adverse reactions (>3%) reported during treatment for CD** are upper respiratory infections, headache, and arthralgia during induction dosing and arthralgia, abdominal pain, injection site reactions, anemia, pyrexia, back pain, arthropathy, and urinary tract infection during maintenance dosing. **Review accompanying risankizumab-rzaa full Prescribing Information for additional information, visit www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110**

See Important Safety Considerations on pages 5-6.

RISN-US-00049-MC Approval date: January 2025 V1.0