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A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis From Digestive Disease Week 2022

A Review of Selected Presentations From DDW 2022

• May 21-24, 2022 • San Diego, California

Special Reporting on:

- Recapture of Response With Ozanimod in Patients With Moderately to Severely Active Ulcerative Colitis Who Withdrew Therapy: Data From the True North Open-Label Extension Study
- Efficacy and Safety of Mirikizumab as Maintenance Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 LUCENT-2 Study
- Long-Term Cardiac Safety of Ozanimod in a Phase 3 Clinical Program of Ulcerative Colitis and Relapsing Multiple Sclerosis
- Efficacy and Safety of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Moderately to Severely Active Ulcerative Colitis: 12-Week Results From the Phase 2 LATTICE-UC Study
- A Randomized Trial of Vedolizumab Dose Optimization in Patients With Moderate to Severe Ulcerative Colitis Who Have Early Nonresponse and High Drug Clearance: The ENTERPRET Trial
- Efficacy and Safety of Extended Induction Treatment With Upadacitinib 45 Mg Once Daily Followed by Maintenance Upadacitinib 15 or 30 Mg Once Daily in Patients With Moderately to Severely Active Ulcerative Colitis
- Upadacitinib Therapy Reduces Ulcerative Colitis Symptoms as Early as Day 1
- Etrasimod 2 mg Once Daily as Treatment for Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials
- Analyses of Data From the Phase 3 True North Trial of Ozanimod: Rapidity of Responses, the Value of Extended Induction, and the Correlation Between Early Responses and Outcomes at 52 Weeks

PLUS Meeting Abstract Summaries

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Recapture of Response With Ozanimod in Patients With Moderately to Severely Active Ulcerative Colitis Who Withdrew Therapy: Data From the True North Open-Label Extension Study

Ozanimod is an oral, selective agonist of the sphingosine-1-phosphate (S1P) receptor that is approved in the United States and Europe for the treatment of moderately to severely active ulcerative colitis (UC).[1,2] Treatment with ozanimod results in the retention of lymphocytes in the peripheral lymphoid organs, preventing their access to sites of chronic inflammation.[3] The US Food and Drug Administration approved ozanimod for UC based on results from the randomized, double-blind phase 3 True North trial.[4] In cohort 1 of the trial, 645 patients with moderately to severely active UC were randomly assigned 2:1 to receive ozanimod (0.92 mg) or placebo.[4] In cohort 2, 367 patients received open-label ozanimod (0.92 mg). Treatment with ozanimod led to significantly higher rates of clinical remission compared with placebo, as both induction (18.4% vs 6.0%; *P*<.001) and maintenance (37.0% vs 18.5%; *P*<.001).[4] The rates of clinical response were also higher with ozanimod than placebo, during both induction (47.8% vs 25.9%; *P*<.001) and maintenance (60.0% vs 41.0%; *P*<.001).

Patients with a clinical response at the end of week 10 were randomly assigned a second time to receive either ozanimod or placebo as maintenance therapy. Patients who developed relapsed UC while receiving placebo during the maintenance period and those who completed the maintenance period through week 52 were offered enrollment into the open-label extension (OLE) phase of the study.

A post hoc analysis evaluated outcomes among patients in the ozanimod arm who achieved a clinical response at week 10, but then relapsed while receiving placebo during the maintenance period and subsequently received reinduction therapy with open-label ozanimod.[5] Disease relapse was defined as a partial Mayo score of at least 4 points, with an increase of at least 2 points from the score at week 10, and an endoscopic score of at least 2 points. Symptomatic clinical response was defined as a reduction from baseline in the symptomatic Mayo score by at least 1 point and at least 30%, with a decrease of at least 1 point in the rectal bleeding score or an absolute rectal bleeding score of 1 or less. Symptomatic clinical response was evaluated at weeks 5 and 10 after the second induction with ozanimod in the OLE.

The True North OLE included 77 patients. The patients' mean age was 40.2±12.9 years, and 55.8% of patients were male. Their mean body mass index (BMI) was 25.1±5.5 kg/m^2. The mean time since UC diagnosis was 7.5±6.5 years, and the mean time since onset of UC symptoms was 8.6±7.7 years. Extensive disease was found in 29.9% of patients, and 70.1% had left-sided disease. The mean total Mayo score was 8.8±1.4. At screening, 41.6% of patients were receiving corticosteroids, and 29.9% of patients had previously used 2 or more biologic therapies. At the end of induction week 10, the patients' mean total Mayo score had decreased from 8.8±1.4 to 3.8±1.6. The rectal bleeding score was 0 in 87.0% of patients. A

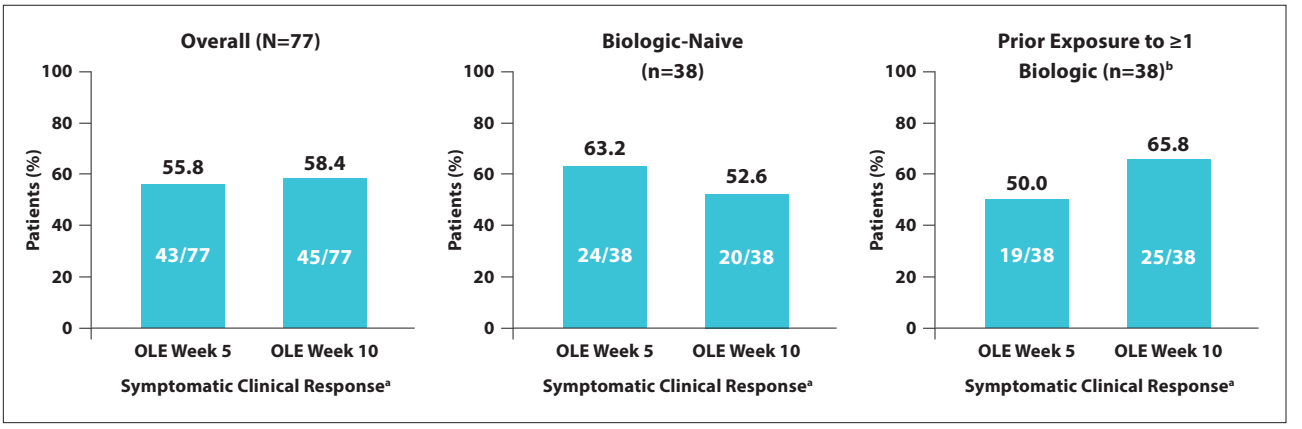

Figure 1. Symptomatic clinical response at OLE weeks 5 and 10 in a post hoc analysis of data from the phase 3 True North trial. This analysis focused on patients treated with ozanimod who achieved a clinical response at week 10, relapsed while receiving placebo during the maintenance period, and subsequently received reinduction therapy with open-label ozanimod. The investigators used a nonresponder imputation analysis. [a]A reduction from study baseline in the symptomatic Mayo score (sum of the RBS and stool frequency subscore) of ≥1 point and ≥30%, and ≥1 point decrease in RBS or absolute RBS ≤1. [b]One patient who was exposed to only a JAK inhibitor was excluded, as they were not considered to be treatment-naive or biologic-exposed. JAK, Janus kinase; OLE, open-label extension; RBS, rectal bleeding subscore. Adapted from Afzali A et al. DDW abstract 969. *Gastroenterology*. 2022;162(suppl 1).[5]

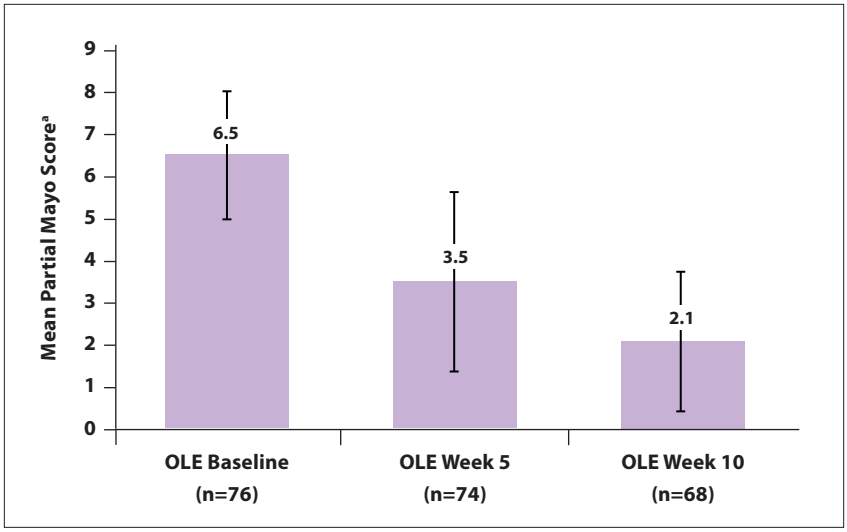

Figure 2. The mean partial Mayo score at OLE in a post hoc analysis of data from the phase 3 True North trial that focused on patients treated with ozanimod who achieved a clinical response at week 10, relapsed while receiving placebo during the maintenance period, and subsequently received reinduction therapy with open-label ozanimod. The error bars represent the standard deviation. [a]The mean partial Mayo score encompasses the sum of the rectal bleeding subscore, the stool frequency subscore, and the Physician's Global Assessment subscore. OLE, open-label extension. Adapted from Afzali A et al. DDW abstract 969. *Gastroenterology*. 2022;162(suppl 1).[5]

stool frequency subscore of 0 or 1 was reported in 80.5% of patients. A Physician's Global Assessment subscore of 0 or 1 was reported in 81.8% of patients.

In the OLE study population of 77 patients who received ozanimod for a second induction, a symptomatic clinical response was reported in 55.8% at week 5 and in 58.4% at week 10 (Figure 1).[5] Among the 38 patients who were biologic-naive at baseline, a symptomatic clinical response was reported in 63.2% at week 5 and in 52.6% at week 10. Among 38 patients with prior exposure to 1 or more biologic therapies at baseline, a symptomatic clinical response was observed in 50.0% at week 5 and 65.8% at week 10. Among 76 evaluable patients, the mean partial Mayo score decreased from 6.5 at the OLE baseline, to 3.5 at OLE week 5, to 2.1 at OLE week 10 (Figure 2). Across the same time points, the rectal bleeding score decreased from 1.5 to 0.6 to 0.2, the stool frequency subscore decreased from 2.6 to 1.6 to 1.0, and the Physician's Global Assessment subscore decreased from 2.4 to 1.4 to 0.9. Study limitations included the small sample size and the post hoc nature of the analysis.

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Efficacy and Safety of Mirikizumab as Maintenance Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 LUCENT-2 Study

Interleukin (IL) 23 is a key cytokine that mediates the inflammatory state of the intestinal mucosa in UC.[1] Mirikizumab is a humanized immunoglobulin G4 monoclonal antibody that attenuates inflammation by binding to subunit p19 of IL-23. The phase 3 LUCENT-1 study compared mirikizumab vs placebo as induction therapy in 1281 patients with UC.[2] The trial met its primary endpoint, showing a superior rate of clinical remission at week 12 with mirikizumab vs placebo (24.2% vs 13.3%; 99.875% CI, 3.2-19.1; *P*=.00006).

LUCENT-2 was a double-blind phase 3 trial that evaluated mirikizumab maintenance therapy in patients with a clinical response to mirikizumab induction therapy at week 12 in LUCENT-1.[3] Enrolled patients were randomly assigned in a 2:1 ratio to receive mirikizumab (200 mg) or placebo every 4 weeks through week 40 of LUCENT-2, for a total of 52 weeks of study treatment. Corticosteroid therapy was tapered starting at week 0 of LUCENT-2. The primary outcome was clinical remission at week 40 of maintenance therapy. Clinical remission was defined as a stool frequency score of 0, or a stool frequency score of 1 with a decrease of at least 1 point from baseline; a rectal bleeding score of 0; and an endoscopic subscore of 0 or 1, excluding friability. Secondary endpoints were also evaluated at week 40 of the trial.

The LUCENT-2 study randomly assigned 365 patients to treatment with mirikizumab and 179 to placebo. The patients' median age was 42 years, and 59% were male. The baseline characteristics were well balanced between the mirikizumab and placebo arms,

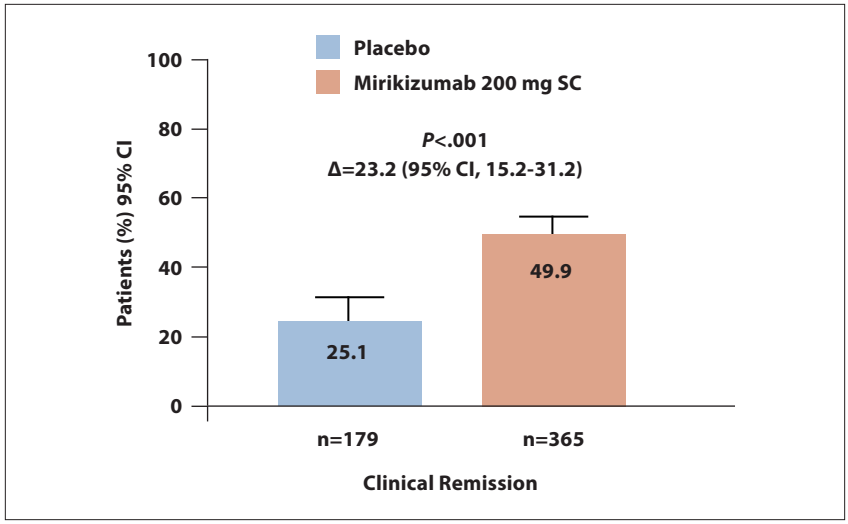

Figure 3. Clinical remission in the double-blind phase 3 LUCENT-2 trial, which evaluated mirikizumab maintenance therapy in patients with moderately to severely active ulcerative colitis who achieved a clinical response to mirikizumab induction therapy at week 12 in the LUCENT-1 trial. SC, subcutaneously. Adapted from Dubinsky MC et al. DDW abstract 867e. *Gastroenterology*. 2022;162(suppl 1).[3]

including disease duration (6.7 vs 6.9 years), median bowel urgency severity (6.0 for both arms), baseline corticosteroid use (37% vs 38%), and baseline immunomodulator use (21% vs 22%). Prior unsuccessful therapies included a biologic agent in 35% of patients and tofacitinib in 36% of patients.

The LUCENT-2 trial met its primary endpoint. Clinical remission was achieved by 49.9% of the mirikizumab arm vs 25.1% of the placebo arm (*P*<.001; Figure 3). The rate of clinical remission at week 40 was 63.6% in the mirikizumab arm vs 36.0% in the placebo arm (95% CI, 10.4%-39.2%; *P*<.001). Moreover, 97.8% of patients in the mirikizumab arm who maintained clinical remission at week 40 were no longer receiving corticosteroids. The rate of corticosteroid-free remission was higher in the mirikizumab arm compared with the placebo arm (*P*<.001). The rate of endoscopic remission was superior with mirikizumab (*P*<.001), as was the rate of histologic-endoscopic mucosal remission (*P*<.001). Treatment with mirikizumab was superior to placebo in maintaining clinical remission at week 40 among patients who were naive to biologic therapy or tofacitinib (*P*<.001) and in patients who had previously received unsuccessful treatment with these agents (*P*<.001). Similarly, mirikizumab led to better endoscopic remission vs placebo in patients without prior exposure to biologic therapy or tofacitinib (*P*<.001) and in those who had received unsuccessful treatment with these agents (*P*<.001). The safety profile of mirikizumab was similar to that observed in prior studies.

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Long-Term Cardiac Safety of Ozanimod in a Phase 3 Clinical Program of Ulcerative Colitis and Relapsing Multiple Sclerosis

Treatment with S1P receptor modulators may be associated with cardiovascular adverse events (AEs), including bradycardia and delays in atrioventricular conduction. The effects of ozanimod on long-term safety were evaluated in a retrospective analysis of UC patients from the phase 3 True North trial and in patients with relapsing multiple sclerosis from the phase 3 SUNBEAM and RADIANCE trials.[1-4]

In the True North trial, patients received treatment with ozanimod at 0.92 mg. Patients in cohort 1 were randomly assigned to receive ozanimod or placebo, whereas patients in cohort 2 received open-label ozanimod. Patients with a clinical response to ozanimod at week 10 were randomly assigned a second time to receive ozanimod or placebo. Patients underwent echocardiogram (ECG) monitoring at screening, day 1, week 10, and week 52. Heart rate was monitored at screening and day 1, and at weeks 5, 10, 18, 28, 40, and 52.

In the SUNBEAM and RADIANCE trials, patients received ozanimod at 2 doses: the standard dose of 0.92 mg and a lower dose of 0.46 mg. ECGs were performed at screening, baseline, day 15, month 12, and, in RADIANCE only, month 24. Heart rate was monitored at screening and baseline visits, on day 15, and every 3 months until the end of treatment.

Key cardiac exclusion criteria for the UC and multiple sclerosis trials included a resting heart rate of less than 55 beats per minute at screening, recent cardiovascular events, and a prolonged corrected QT interval. The trials excluded patients who were receiving concurrent therapy with QT-prolonging medications.

In all of the studies, continuous treatment with ozanimod did not lead to clinically significant changes in ECG results or heart rate. In the True North trial, the mean change in heart

Table 1. Cardiac-Related TEAEs Among Patients With Ulcerative Colitis Who Received Ozanimod or Placebo During the Induction Period of the Phase 3 True North Trial

	Induction		
	Cohort 1		Cohort 2
TEAE (n%)	Placebo (n=216)	Ozanimod, 0.92 mg (n=429)	Ozanimod, 0.92 mg (n=367)
Cardiac Disorders	2 (0.9)	6 (1.4)	8 (2.2)
Bradycardia	0	2 (0.5)	3 (0.8)
Palpitations	0	2 (0.5)	1 (0.3)
Tachycardia	0	2 (0.5)	1 (0.3)
Angina pectoris	1 (0.5)	0	1 (0.3)
Atrial fibrillation	0	0	1 (0.3)
Coronary artery stenosis	0	0	1 (0.3)
Sinus bradycardia	0	0	1 (0.3)
Ventricular extrasystoles	1 (0.5)	0	0

TEAEs, treatment-emergent adverse events.
Adapted from Long MD et al. DDW abstract 15. *Gastroenterology*. 2022;162(suppl 1).[3]

rate from baseline to week 52 was –1.0 beat per minute (Figure 4). During the induction period, 6 patients (1.4%) in cohort 1 developed a treatment-emergent cardiac AE, including 2 patients (0.5%) with bradycardia (Table 1). In cohort 2, 8 patients (2.2%) developed a treatment-emergent cardiac AE, including 3 patients (0.8%) with bradycardia. During maintenance treatment, 3 patients (1.3%) experienced a treatment-emergent cardiac AE. There were no reports of bradycardia. Treatment-emergent cardiac AEs were more common in patients with a history of cardiovascular disease vs those without (3.5% vs 0.6%).

The ECGs showed no significant changes in PR, QRS, or QT intervals. There were no cases of second- or third-degree heart block.

Among patients with multiple sclerosis enrolled in the SUNBEAM and RADIANCE studies, continual treatment with ozanimod through month 24 was not associated with clinically significant changes in ECG results or heart rate. Among 882 patients, a treatment-emergent cardiac AE was reported in 30 (3.4%), including 7 patients (0.8%) with bradycardia. The rate of treatment-emergent cardiac AEs was 3.5% in patients with a history of cardiovascular disease vs 3.4% in those without. In 2 patients (0.2%), a serious treatment-emergent cardiac AE required hospitalization.

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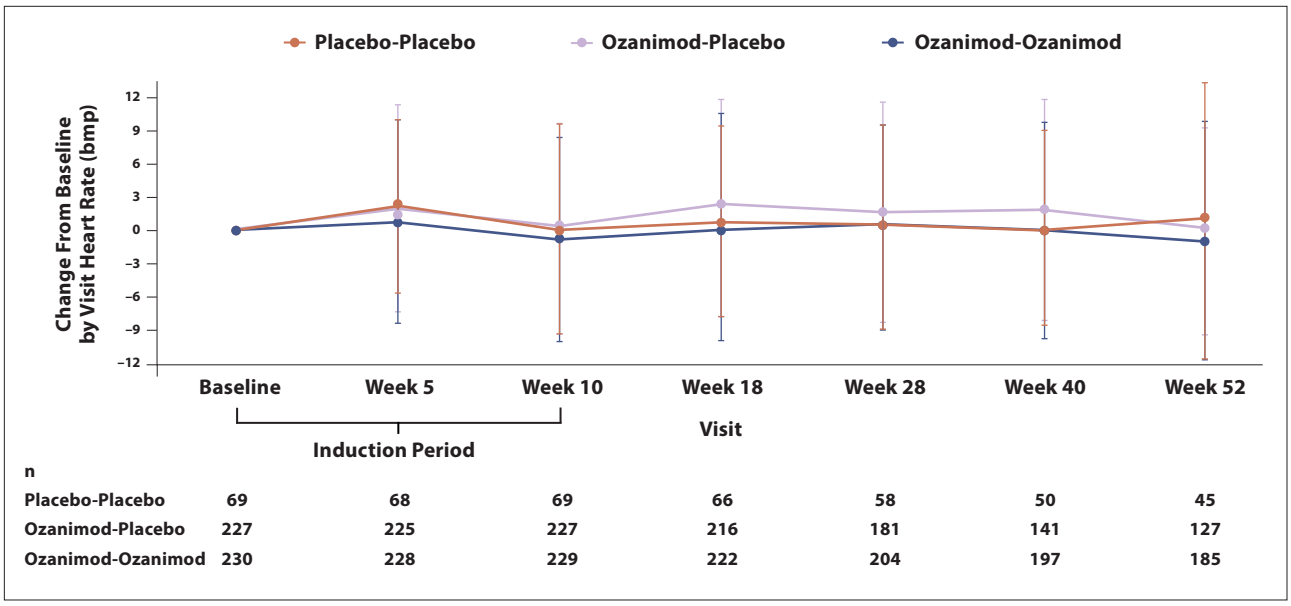

Figure 4. The impact of continuous ozanimod treatment on heart rate among patients with ulcerative colitis during the maintenance period of the phase 3 True North trial. bpm, beats per minute. Adapted from Long MD et al. DDW abstract 15. *Gastroenterology*. 2022;162(suppl 1).[3]

Efficacy and Safety of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Moderately to Severely Active Ulcerative Colitis: 12-Week Results From the Phase 2 LATTICE-UC Study

Deucravacitinib is an allosteric inhibitor of tyrosine kinase 2 (TYK2), which plays a role in adaptive and innate immunity.[1] This inhibitor has a mechanism of action that is distinct from the other Janus kinase (JAK) inhibitors. Deucravacitinib selectively impedes human immune cells from responding to IL-12, IL-23, or type I interferon. In a mouse model of inflammatory bowel disease, deucravacitinib demonstrated efficacy that was consistent with inhibition of autoimmunity. Deucravacitinib was effective in phase 2 and 3 trials of patients with psoriatic arthritis or plaque psoriasis.[2,3]

LATTICE-UC was a double-blind phase 2 study that investigated the safety and efficacy of deucravacitinib in patients with moderately to severely active UC who had experienced an inadequate response or loss of response or who were intolerant to 1 or more conventional or biologic therapies.[4] After a 4-week screening period, 131 patients were randomly assigned to receive deucravacitinib (6 mg twice daily) or placebo. The primary endpoint was clinical remission at week 12. Clinical remission was defined as a modified Mayo score with a stool frequency subscore of 1 or less and with a decrease from baseline of at least 1 point, a rectal bleeding subscore of 0, and an endoscopy subscore of 1 or less.

The baseline characteristics were generally similar in the 2 arms. There were differences between the treatment arms for the patients' weight (≤90 kg, 25.0% in the deucravacitinib arm vs 16.3% in the placebo arm), modified Mayo score (≤7, 64.8% vs 72.1%, respectively), and endoscopic subscore (median of 3.0 [range, 2-3] vs 2.0 [range, 1-3], respectively).

At week 12, the rates of clinical remission were 14.8% in the deucravacitinib arm vs 16.3% in the placebo arm (*P*=.59; Figure 5). Among patients without prior exposure to biologic therapy, the rates of clinical remission were 14.0% with deucravacitinib vs 25.9% with placebo. However, in patients with prior exposure to at least 1 biologic therapy, the rates of clinical remission were higher with deucravacitinib compared with placebo (16.1% vs 0.0%, respectively). The rates of endoscopic response were similar in the deucravacitinib arm and the placebo arm in the overall population (*P*=.88), as well as in subgroups with or without prior exposure to biologic therapy.

The trial failed to meet its primary and secondary endpoints. In the overall population, treatment with deucravacitinib led to a numerical improvement in the symptomatic Mayo score from baseline compared with placebo (–2.2 vs –1.6). Most AEs were mild to moderate in severity. Serious AEs occurred in 9.2% of patients in the deucravacitinib arm. A second phase 2 trial will evaluate a higher dose of deucravacitinib in patients with UC.

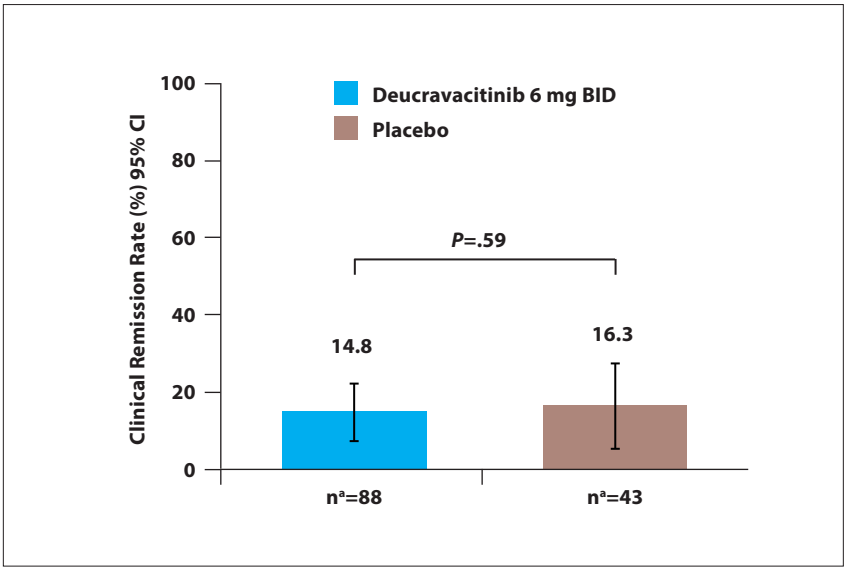

Figure 5. Rates of clinical remission at 12 weeks among patients with moderately to severely active ulcerative colitis treated with deucravacitinib or placebo in the phase 2 LATTICE-UC study. [a]The numbers of patients were based on the electronic case report form. BID, twice daily. Adapted from Danese S et al. DDW abstract 965. *Gastroenterology*. 2022;162(suppl 1).[4]

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A Randomized Trial of Vedolizumab Dose Optimization in Patients With Moderate to Severe Ulcerative Colitis Who Have Early Nonresponse and High Drug Clearance: The ENTERPRET Trial

The biologic agent vedolizumab is a humanized monoclonal antibody that binds to integrin α4β7.[1] Research has suggested that primary or secondary failure to respond to biologic therapies might result from suboptimal drug concentrations in the blood and higher rates of drug clearance.[2-4] The open-label, phase 4 ENTERPRET study of vedolizumab in UC compared a dose-optimization strategy vs standard dosing in patients who had high drug clearance and who exhibited a primary nonresponse to vedolizumab after 5 weeks of standard therapy.[5] The primary endpoint was endoscopic mucosal healing at week 30, which was defined as a Mayo endoscopic subscore of 1 point or less, excluding friability, by central reading.

The trial treated 278 patients with the standard dose of vedolizumab.[5] At the end of week 5, 108 patients had a serum vedolizumab level of less than 50 µg/mL. These patients were randomly assigned to receive vedolizumab at the standard dose (n=53) or with dose optimization (n=55). In the dose-optimization arm, patients with a serum concentration of at least 30 µg/mL but less than 50 µg/mL received 600 mg of vedolizumab at week 6, followed by 300 mg every 4 weeks (regimen A). Patients with a vedolizumab serum concentration of less than 30 µg/mL received 600 mg of vedolizumab at week 6, followed by 600 mg every 4 weeks (regimen B). The patients' baseline characteristics were similar between the 2 randomized arms. However, a greater proportion of patients in the dose-optimization arm had severe UC at baseline (61.8% vs 47.2%).

The ENTERPRET trial did not meet its primary endpoint. Endoscopic mucosal healing at week 30 was achieved by 18.9% of patients in the standard-dose arm vs 14.5% of patients in the dose-optimization arm (*P*=.561).[5] Rates of endoscopic mucosal healing at week 30 were also similar when standard dosing was compared with regimen A (*P*=.612) and regimen B (*P*=.666; Figure 6). Rates of clinical remission at week 30, clinical response at week 30, clinical response at week 14, and durable clinical response were all similar with standard dosing vs dose optimization, and when standard dosing was compared with regimen A and regimen B (*P*>.1 for all comparisons).

There were no new safety signals in the study. AEs were more common in the dose-optimized arm. Serious AEs were equivalent between the arms.

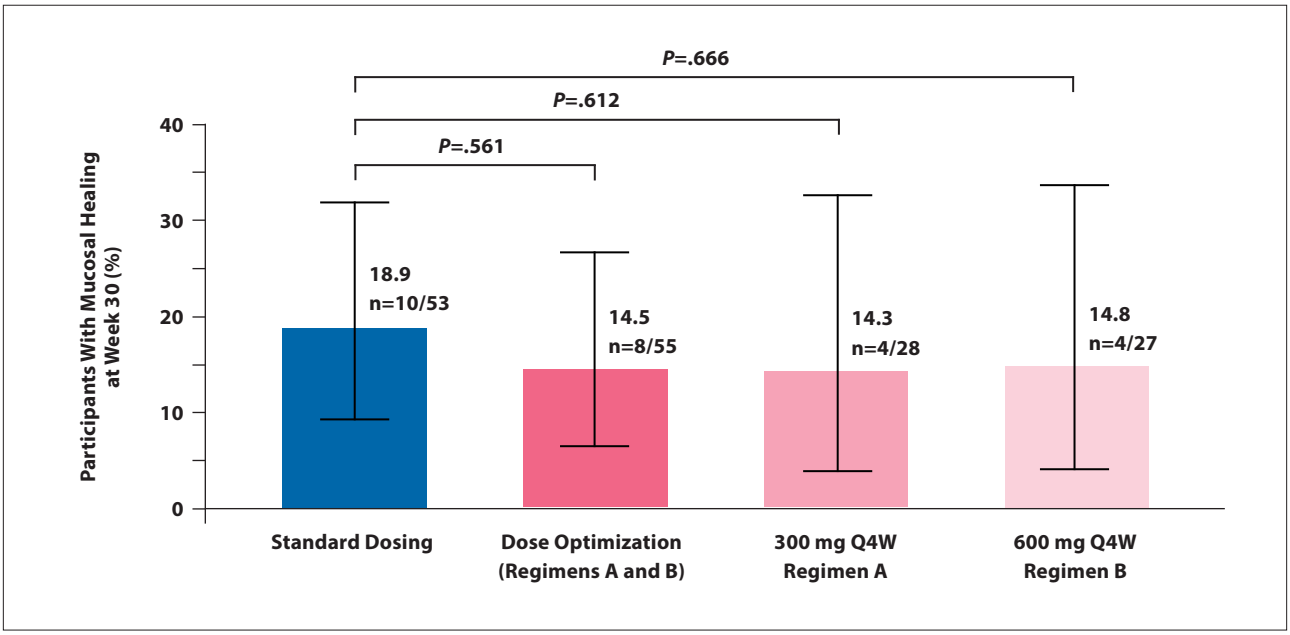

Figure 6. Mucosal healing in the phase 4 ENTERPRET study, which compared vedolizumab administered in a dose-optimization strategy vs standard dosing in patients with moderate to severe ulcerative colitis who had high drug clearance and who had exhibited a primary nonresponse to vedolizumab after 5 weeks of standard therapy. Regimen A was administered to patients with a serum concentration of at least 30 µg/mL but less than 50 µg/mL and consisted of 600 mg of vedolizumab at week 6, followed by 300 mg every 4 weeks. Regimen B was administered to patients with a vedolizumab serum concentration of less than 30 µg/mL and consisted of 600 mg of vedolizumab at week 6, followed by 600 mg every 4 weeks. Q4W, every 4 weeks. Adapted from Yarur A et al. DDW abstract 791. *Gastroenterology*. 2022;162(suppl 1).[5]

The safety profile in the cohort that received dose-optimized vedolizumab was comparable to that observed with standard dosing in previous randomized trials. The most common AE was exacerbation of UC, which occurred in 9.4% of patients in the standard dosing arm and 14.8% of patients receiving dose-optimized regimen B. Other events included an increased levels of C-reactive protein and cases of upper respiratory tract infection, which is consistent with previous clinical trials.

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Efficacy and Safety of Extended Induction Treatment With Upadacitinib 45 Mg Once Daily Followed by Maintenance Upadacitinib 15 or 30 Mg Once Daily in Patients With Moderately to Severely Active Ulcerative Colitis

Upadacitinib is a reversible JAK inhibitor with increased selectivity for JAK1 compared with JAK2, JAK3, and TYK2.[1] Phase 2b and phase 3 clinical studies demonstrated the safety and efficacy of an 8-week course of upadacitinib (45 mg daily) as induction therapy among patients with moderately to severely active UC.[2-5]

A study examined whether 16 weeks of extended induction treatment with upadacitinib could benefit patients with moderately to severely active UC who did not have a clinical response after 8 weeks of induction therapy.[6] In the phase 3 U-ACHIEVE and U-ACCOMPLISH trials, 125 patients did not obtain a clinical response after 8 weeks of induction therapy with upadacitinib (45 mg daily).[2,4] These patients received open-label upadacitinib at the same dose for another 8 weeks. Patients who responded to extended induction therapy were randomly assigned to receive daily upadacitinib at a dose of 15 mg (n=21) or 30 mg (n=24) as maintenance therapy in the 52-week U-ACHIEVE maintenance study.

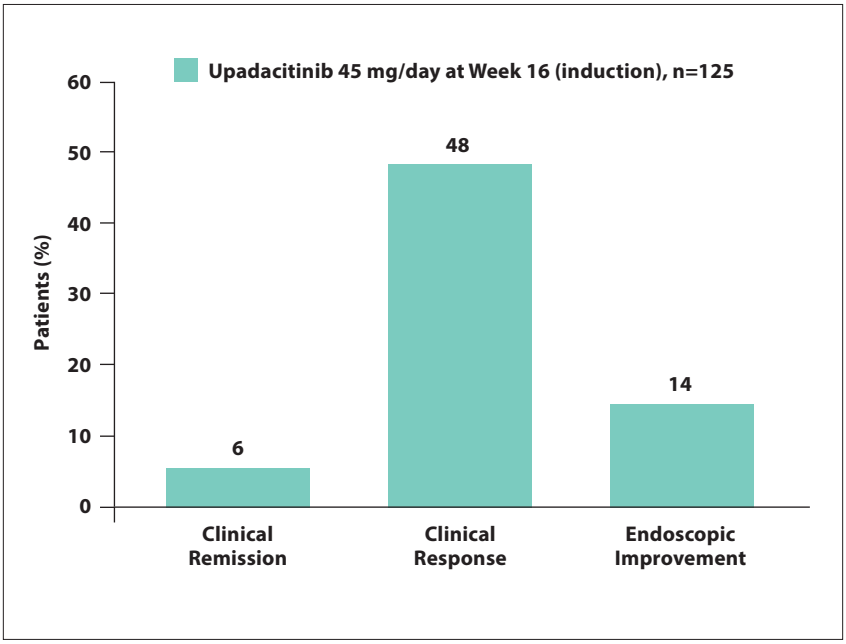

Figure 7. Efficacy of 16 weeks of extended induction treatment with upadacitinib in patients with moderately to severely active ulcerative colitis. Adapted from Vermeire S et al. DDW abstract 966. *Gastroenterology*. 2022;162(suppl 1).[6]

The 125 patients who entered the extended induction treatment period were a median age of 43.1±15.45 years. Their mean BMI was 24.3±4.06 kg/m^2, and the mean disease duration was 6.71±5.92 years. Among the patients without a response to an 8-week course of induction therapy with upadacitinib, 48% exhibited a clinical response after 16 weeks of induction therapy (Figure 7).[6] A clinical remission was reported in 6% of these patients. At the end of the 52-week maintenance period, a dose-response effect was observed with the higher dose vs the lower dose of upadacitinib as measured by rates of clinical response (67% vs 36%), clinical remission (33% vs 19%), and endoscopic improvement (38% vs 24%).

Among the patients who received upadacitinib for 52 weeks, serious AEs occurred in 10.0% of the high-dose group and 2.9% of the low-dose group. AEs required treatment discontinuation in 5.0% vs 2.9% of patients, respectively. Severe AEs occurred in 5.0% vs 0%. Among patients who

received the higher dose of upadacitinib for 52 weeks, the most common AEs of special interest were anemia (7.5%) and hepatic disorder (7.5%).

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Upadacitinib Therapy Reduces Ulcerative Colitis Symptoms as Early as Day 1

Unpredictable symptoms, such as diarrhea and bowel urgency, significantly reduce quality of life among patients with UC.[1] The U-ACHIEVE and U-ACCOMPLISH trials were both double-blind, multicenter, randomized, placebo-controlled phase 3 studies that compared 8 weeks of upadacitinib (45 mg daily) vs placebo in patients with moderately to severely active UC.[2-4] Both trials achieved their common primary endpoint of an improvement in clinical remission among patients treated with upadacitinib vs placebo, as well as all secondary endpoints.

A post hoc analysis evaluated the efficacy of upadacitinib (45 mg daily) on daily improvement of UC symptoms.[5] Achievement of clinical remission according to an adapted Mayo score at week 8 corresponded to a stool frequency score of 1 or lower on day 7 (odds ratio, 2.61; 95% CI, 1.64-4.15) and to the absence of bowel urgency on day 7 (odds ratio, 2.34; 95% CI, 1.48-3.70). Demonstration of a clinical response (based on an adapted Mayo score at week 8) was associated with a stool frequency score of 1 or lower on day 7 (odds ratio, 2.48; 95% CI, 1.56-3.93). On day 1 of treatment, patients who received upadacitinib exhibited significant improvements in their stool frequency score and their rectal bleeding score (Figure 8). Treatment with upadacitinib significantly improved (P<.05) abdominal pain and bowel urgency as early as day 3. The rate of clinical remission was significantly higher by week 2 with upadacitinib vs placebo (P≤.001), and this rate remained higher through week 8. Similarly, a significantly higher proportion of patients who received upadacitinib achieved a clinical response at week 2 compared with placebo (P≤.001). This difference persisted through week 8.

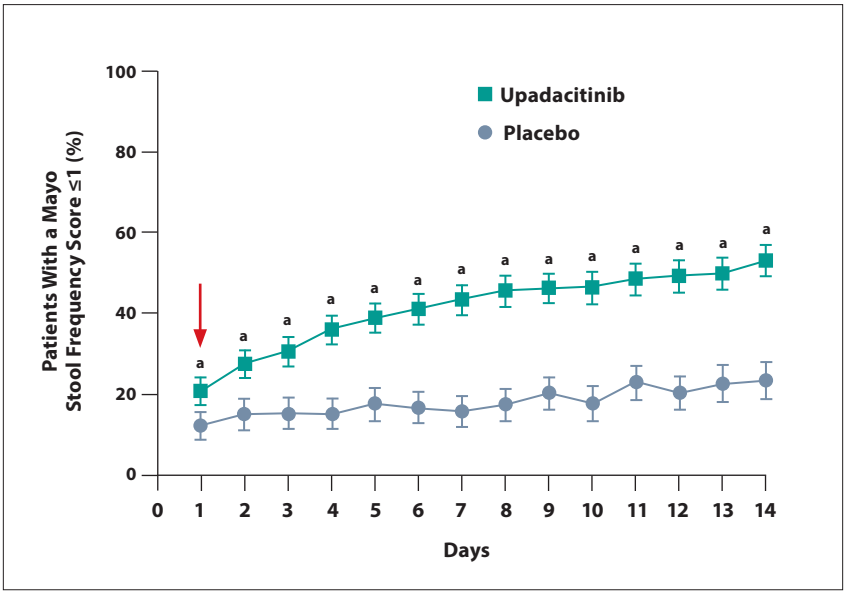

Figure 8. Patients with a Mayo stool frequency score of ≤1 in a post hoc analysis of the U-ACHIEVE and U-ACCOMPLISH trials, which compared 8 weeks of upadacitinib vs placebo in patients with moderately to severely active ulcerative colitis. [a]P≤.001 vs placebo. Adapted from Vermeire S et al. DDW abstract 967. *Gastroenterology*. 2022;162(suppl 1).[5]

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Etrasimod 2 mg Once Daily as Treatment for Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials

Etrasimod is an investigational, oral S1P receptor modulator that demonstrated efficacy in a phase 2 trial of patients with moderately to severely active UC.[1,2] The double-blind phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials evaluated the safety and efficacy of etrasimod (2 mg daily) in patients with UC.[3] The trial enrolled patients ages 16 to 80 years with UC that was confirmed by endoscopy and histopathology, with at least 10 cm of rectal involvement. The patients had moderately to severely active UC based on a modified Mayo score of 4 to 9 and a documented history of an inadequate response to, loss of response to, or intolerance to 1 or more treatments for UC. The trial excluded patients with previous exposure to more than 2 biologic therapies or 1 biologic agent plus an approved JAK inhibitor. The primary endpoints of the ELEVATE UC 52 trial were clinical remission at week 12 and clinical remission at week 52. The primary endpoint of the ELEVATE UC 12 trial was clinical remission at week 12.

The ELEVATE UC 52 study randomly assigned 289 patients to etrasimod (2 mg daily) and 144 to placebo. In the etrasimod arm, 265 patients (91.7%) completed week 12 of treatment and 161 patients (55.7%) completed week 52 of treatment. Among patients in the placebo arm, 124 (86.1%) completed week 12 and 46 (31.9%) completed week 52.

At week 12, the rate of clinical remission was 27.0% in the etrasimod arm vs 7.4% in the placebo arm (P<.001; Figure 9). At week 52, the rate of clinical remission was 32.1% with etrasimod vs 6.7% with placebo (P<.001).

The trial also met its secondary endpoints. At weeks 12 and 52, treatment with etrasimod led to endoscopic improvement, symptomatic remission, mucosal healing, and clinical response (P<.001). Sustained clinical remissions were observed in 17.9% of the etrasimod arm vs 2.2% of the placebo arm. Sustained clinical remissions were observed in 17.9% vs 2.2% of patients, respectively (P<.001). Corticosteroid-free remission at 12 weeks was reported in 32.1% vs 6.7% of patients, respectively (P<.001).

The ELEVATE UC 12 trial randomly assigned 238 patients to etrasimod (2 mg daily) and 116 patients to placebo. Week 12 of treatment was completed by 213 patients (89.5%) in the etrasimod arm and 103 patients (88.8%) in the placebo arm. The trial met its primary endpoint by demonstrating a 12-week rate of clinical remission of 24.8% with etrasimod vs 15.2% with placebo (P=.0264). Treatment with etrasimod was also significantly better compared with placebo based on measures such as endoscopic improvement (P=.0092), symptomatic remission (P=.0013), mucosal healing (P=.0358), and clinical response (P<.001).

Rates of treatment-emergent AEs and serious AEs were generally similar between both arms in the 2 trials. The most frequently reported treatment-emergent AEs of any grade among patients treated with etrasimod were headache, worsening of UC, COVID-19, and dizziness.

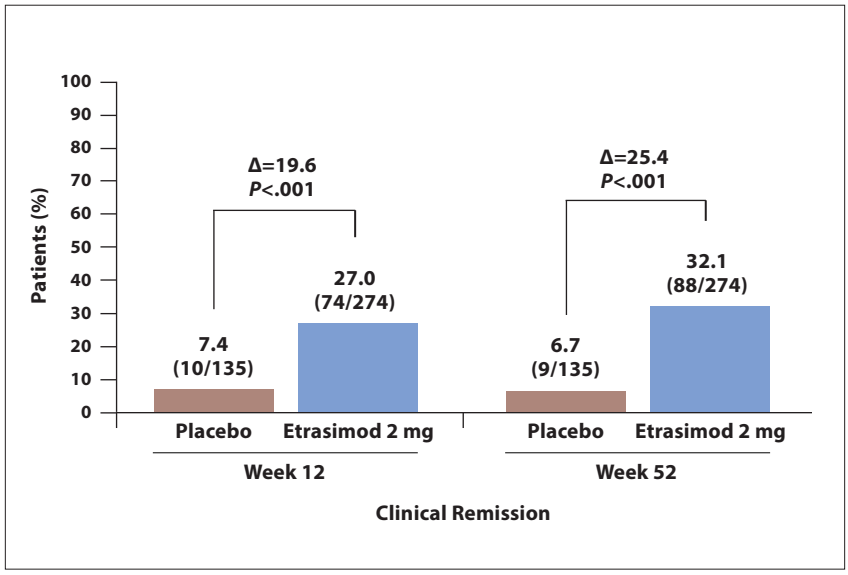

Figure 9. Clinical remission among patients with moderately to severely active ulcerative colitis in the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials, which evaluated etrasimod. Clinical remission was defined as a stool frequency subscore of 0 (or 1 with a ≥1 point decrease from baseline), a rectal bleeding subscore of 0, and an endoscopic subscore of ≤1 (excluding friability). Adapted from Sandborn WJ et al. DDW abstract 968a. *Gastroenterology*. 2022;162(suppl 1).[3]

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Analyses of Data From the Phase 3 True North Trial of Ozanimod: Rapidity of Responses, the Value of Extended Induction, and the Correlation Between Early Responses and Outcomes at 52 Weeks

Three analyses of data from the True North trial demonstrated the rapidity of responses from ozanimod, the value of extended induction with ozanimod, and the correlation between early responses and outcomes at 52 weeks.[1] In cohort 1, the rate of symptomatic response was superior with ozanimod vs placebo as early as week 2 of treatment (36.1% vs 26.4%; 95% CI, 2.1%-17.0%; Figure 10).[2] A superior rate of response with ozanimod vs placebo was observed as early as 2 weeks after initiation of treatment in patients without prior exposure to a tumor necrosis factor (TNF) inhibitor and as early as 4 weeks after initiation of treatment in patients with prior exposure to a TNF inhibitor.

Among the overall study population, symptomatic remission 5 weeks after the initiation of treatment was reported in 26.3% of the ozanimod arm vs 16.7% of the placebo arm (95% CI, 1.8%-15.4%). In cohort 1, 150 patients did not have a clinical response at week 10 and entered the OLE study.[3] Despite a lack of clinical response, these patients experienced a reduction in their mean total Mayo score from 9.2±1.3 at baseline to 8.5±1.6 at week 10. The rate of patients with a rectal bleeding score of 0 increased to 23.3% at week 10 from 0.7% at baseline. At week 10 of the OLE, 48.7% of patients had a symptomatic clinical response.

At week 10 of the induction period in the True North trial, 44 patients had mucosal healing (defined as a Geboes score of <2.0) and 186 did not.[4] Among patients treated with ozanimod, mucosal healing at week 10 corresponded to improved clinical, endoscopic, and histologic outcomes at week 52. Patients with mucosal healing at week 10 had a higher rate of clinical remission (52.9% vs 38.3%), corticosteroid-free remission (50.0% vs 32.5%), mucosal healing (55.9% vs 25.8%), endoscopic improvement (70.6% vs 45.0%), and histologic remission (61.8% vs 29.2%) at week 52 compared with patients who did not have mucosal healing at week 10.

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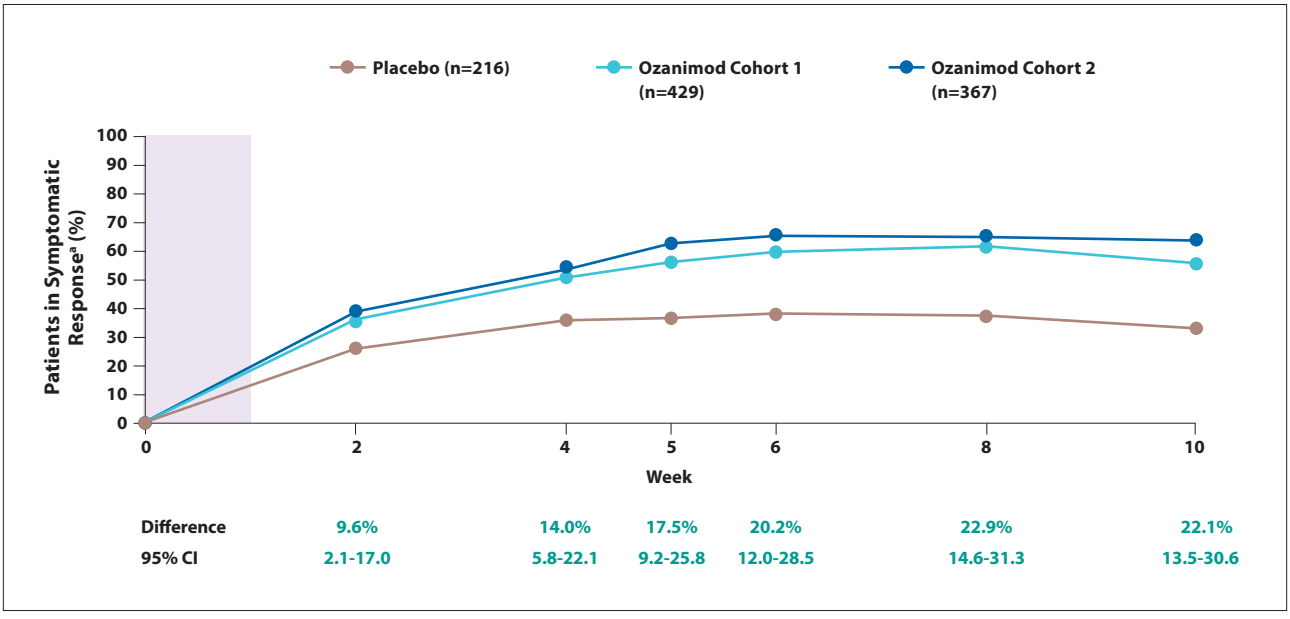

Figure 10. Symptomatic response through week 10 among TNFi-naive patients who received ozanimod during the induction period of the phase 3 True North trial. RBS, rectal bleeding subscore; SFS, stool frequency subscore; TNFi, tumor necrosis factor inhibitor. [a]Decrease from baseline of ≥1 point and ≥30% in the adapted partial Mayo score (sum of RBS, SFS, and Physician Global Assessment subscore, ranging from 0-9 points) and a decrease of ≥1 point from baseline in RBS or an absolute RBS ≤1 point. Adapted from Afzali A et al. DDW abstract Tu1472. *Gastroenterology*. 2022;162(suppl 1).[2]

Highlights in Ulcerative Colitis From Digestive Disease Week 2022: Commentary

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Multiple presentations at Digestive Disease Week (DDW) 2022 provided novel insights into the management of ulcerative colitis (UC). Data were presented for existing and emerging agents, including vedolizumab, mirikizumab, tofacitinib, upadacitinib, ozanimod, etrasimod, and deucravacitinib.

Vedolizumab

A main theme of ongoing studies in inflammatory bowel disease concerns the choice of therapy and sequencing of therapies. Emerging studies aim to discover whether use of one treatment mechanism before another has a rationale based on the likelihood of response. Studies are also exploring subsequent treatments in patients who did not respond or who lost response to an earlier therapy. Selection of a secondary treatment depends on factors including the disease duration, prior treatment exposures, and the presence of concomitant immune conditions, such as psoriasis or joint problems. Presentations at DDW 2022 included results from studies that evaluated the efficacy of available or emerging agents in treating concomitant diseases and studies that explored sequencing of therapies. One example is the RALEE study, which examined a claims database to compare the response to vedolizumab in patients with UC who received early vs delayed treatment.[1] Dr Noa Krugliak Cleveland and colleagues identified that patients who received vedolizumab within 30 days of their diagnosis had higher persistence on therapy compared with patients who received 5-aminosalicylates, corticosteroids, or immunomodulators before they initiated therapy. Persistence on therapy is a surrogate in claims analyses of efficacy. The RALEE study is one of the first and largest studies to suggest that disease duration or time related to treatment sequencing may have the same impact on treatment response in UC as previously reported in Crohn's disease.[2] The message for clinicians is that when a patient presents with moderate to severe UC, it is important to initiate an effective therapy early and bring the disease under control. This strategy will not only help the patient feel better quickly, but it may also improve the likelihood of a response.

There is ongoing discussion and some debate about the value of proactive dose optimization of biologic therapies. Most studies have explored this issue in patients receiving infliximab, an anti–tumor necrosis factor (TNF) therapy.[3] The ENTEPRET trial examined dose optimization of vedolizumab in patients with UC who had an early nonresponse to therapy with high drug clearance.[4] This important study explored whether use of vedolizumab dose optimization could improve overall response. The primary endpoint was endoscopic mucosal healing at week 30. In the study design, patients who did not have a clinical response at week 6 and who had high drug clearance at week 5 were randomly assigned to receive vedolizumab at the standard dose of 300 mg intravenously (IV) every 8 weeks or to 1 of 2 dose-optimized strategies until week 26. The dose optimization strategy was based on the patient's drug level. If the patient's drug level was between 30 µg/mL and less than 50 µg/mL at week 5, the dose was increased to 600 mg IV at 6 weeks and then decreased to 300 mg IV every 4 weeks afterward. Patients whose drug level was less than 30 µg/mL at week 5 received a single 600-mg dose at week 6 and continued to receive 600 mg every 4 weeks afterward.

Patients who had a primary nonresponse at week 6 and had high drug clearance did not achieve better results with dose optimization compared with standard dosing (300 mg every 8 weeks). This finding suggests that dose optimization in the setting of primary nonresponse to vedolizumab may not benefit patients. This study does not address whether patients who respond early to therapy and then lose response later—the so-called attenuation of response—might still benefit from dose escalation. In my practice, similar to these findings, I have observed that patients who do not respond to vedolizumab after the loading dose do not benefit from subsequent dose escalation. In contrast, patients who respond to therapy at first, but then lose the response, may benefit from dose escalation.

Mirikizumab

The randomized phase 3 LUCENT-1 trial compared the selective interleukin (IL) 23 inhibitor mirikizumab with placebo among patients with moderately to severely active UC.[5] Mirikizumab was administered at 300 mg IV every 4 weeks. The primary outcome was clinical remission at week 12. The trial demonstrated that mirikizumab was superior to placebo in achieving the primary endpoint of clinical remission, as well as in key secondary endpoints measuring clinical, endoscopic, histologic, and symptomatic outcomes. Mirikizumab works well in patients who are biologic-naive, as well as in patients who have failed multiple biologic therapies. Like the other IL-23 inhibitors, mirikizumab has a very acceptable safety profile.

LUCENT-2 was a double-blind phase 3 trial that enrolled patients who achieved a clinical response to induction therapy with mirikizumab in the LUCENT-1 study.[6] The patients were randomly assigned to receive mirikizumab at 200 mg subcutaneously or placebo every 4 weeks to week 52; these patients therefore received 12 weeks of induction followed by 40 weeks of maintenance. The primary endpoint of the study was clinical remission and maintenance of clinical remission.

Mirikizumab was highly effective at achieving this endpoint. The maintenance remission rate was 63.6% with mirikizumab compared with 36.9% with placebo. In these randomized responder studies, placebo rates are often high in the maintenance setting because the patients had received active drug in the induction phase, and benefits carry over. Also of note in the maintenance LUCENT-2 study was that the secondary endpoints of endoscopic remission and histo-endoscopic mucosal remission were superior to placebo as objective measures of disease response. In addition, 98% of the mirikizumab-treated patients in clinical remission at week 40 were not receiving treatment with corticosteroids. Mirikizumab is of great interest as an additional IL-23 inhibitor, and hopefully it will receive FDA approval from the US Food and Drug Administration (FDA) for UC in the near future.

Tofacitinib

Tofacitinib is a pan–Janus kinase (JAK) inhibitor that is FDA-approved for patients with moderately to severely active UC who received unsuccessful treatment with an anti-TNF therapy. Dr William Sandborn and colleagues presented a study of safety data from the OCTAVE and RIVETING trials of tofacitinib in UC.[7] This analysis is of particular importance due to the previously published ORAL Surveillance study in patients with rheumatoid arthritis and preexisting cardiovascular disease, which suggested that patients receiving tofacitinib had a higher rate of venous thromboembolic complications, cardiovascular events, and malignancies as compared with those receiving a TNF inhibitor.[8] There has been ongoing discussion about whether this finding also applies to the UC population. These risks might instead be unique to the high-risk population of rheumatoid arthritis patients, who were receiving concomitant methotrexate and had preexisting cardiovascular disease. In addition, those who developed lung cancer were smokers, something else we rarely see in patients with UC.

In this analysis presented at the DDW of patients with UC, the safety of tofacitinib was consistent with that of other treatments in this setting, including biologic therapies. An exception was an increased incidence of herpes zoster, which has been reported with all JAK inhibitors. Thromboembolic events are a known complication of UC.[9] However, this long-term analysis did not show an increase in venous thromboembolic complications. Patients with high-risk rheumatoid arthritis may be a unique population, owing to the use of concomitant methotrexate or another factor. Overall, this long-term safety analysis provides reassurance for the use of tofacitinib in patients with moderate to severe UC who had

ABSTRACT SUMMARY Tofacitinib for the Treatment of Ulcerative Colitis: An Integrated Summary of Safety Data From the Global OCTAVE and RIVETING Clinical Trials

A retrospective analysis evaluated safety results with tofacitinib in UC patients enrolled in completed phase 2, phase 3, and OLE studies, as well as an ongoing phase 3b/4 study (Abstract 968). The maintenance cohort included 198 patients treated with placebo, 198 treated with tofacitinib at 5 mg twice daily, and 196 treated with tofacitinib at 10 mg twice daily. The total exposure was approximately 3 times greater among patients who received the higher dose of the study drug. The ongoing phase 3b/4 study includes 202 patients treated with tofacitinib at 5 mg twice daily and 955 treated with tofacitinib at 10 mg twice daily. Incidence rates were generally less than 2% for AEs of special interest, such as infections, gastrointestinal perforations, deep vein thrombosis, pulmonary embolism, and major adverse cardiovascular events. The incidence rate for herpes zoster infection was 6.64 among patients in the maintenance cohort treated with tofacitinib at 10 mg twice daily. Incidence rates for AEs of special interest remained stable over a period of up to 7.8 years.

received unsuccessful treatment with at least 1 anti-TNF therapy. Ongoing screening for individual risks of venous thromboembolic complications is recommended. However, the risk seen in high-risk rheumatoid arthritis patients has not changed the general use of tofacitinib in patients with UC.

Upadacitinib

Upadacitinib is a selective JAK-1 inhibitor that also confers some JAK-2 inhibition. Upadacitinib was recently approved by the FDA for the treatment of moderately to severely active UC after unsuccessful anti-TNF therapy. Several ongoing studies and subset analyses are evaluating the efficacy of upadacitinib in UC. In the phase 3 induction studies, upadacitinib had a very predictable pharmacokinetic profile, as a small molecule that is absorbed in the small bowel, and had a rapid onset.[10,11]

Dr Séverine Vermeire and colleagues presented an analysis of data from the phase 3 U-ACHIEVE and U-ACCOMPLISH trials that focused on the onset of efficacy.[12] The study found that some patients had improvement in stool frequency and abdominal pain as early as 1 day after starting therapy. By day 3, upadacitinib was associated with significant improvements in bowel urgency, return of stool frequency to baseline, and absence of rectal bleeding compared with placebo. These findings demonstrate the speed of onset of the mechanism and delivery system of upadacitinib. They also suggest that it might be possible to administer upadacitinib without concomitant corticosteroids as a bridge to help patients feel better. In clinical practice, I tell patients that they should expect to know within the first week of therapy whether upadacitinib is helping them and whether treatment is likely to lead to a complete remission by the end of 8 weeks. Although some patients have an immediate response to upadacitinib and do well, others may need a longer course of therapy to achieve the desired outcome.

ABSTRACT SUMMARY Early vs Delayed Initiation of Vedolizumab in Ulcerative Colitis: Treatment Response in the Real World (RALEE)

The observational RALEE study evaluated the impact of initial treatment with immunomodulators, corticosteroids, and/or 5-aminosalicylates on the response to treatment with vedolizumab in UC patients (Abstract Mo1551). Among 136,315 patients identified in 2 medical databases, 1342 had received treatment with vedolizumab and met the selection criteria. Patients who received vedolizumab within 30 days of diagnosis were more likely to achieve a response to treatment with the antibody compared with patients who began treatment after receiving an immunomodulator, a corticosteroid, and/or 5-aminosalicylates (88.8% vs 70.1%-79.8%). The results were consistent with guidelines that recommend vedolizumab as induction treatment in patients with moderately to severely active UC (Rubin DT et al. *Am J Gastroenterol*. 2019;114[3]:384-413).

Dr Vermeire also presented results from a study that examined the utility of administering upadacitinib for longer than the standard 8 weeks of induction in certain patients.[13] The terms "delayed response" and "delayed remission" describe a known situation in which treatment for the initial 8 weeks has minimal response, but continuing treatment for an additional 8 weeks may be beneficial. In the pivotal trials of upadacitinib in UC, an additional 8 weeks of therapy was available in the open-label extension.[10,11] After the additional 8 weeks, these patients entered the maintenance study. They were then randomly assigned to receive upadacitinib at a daily dose of 15 mg or 30 mg for up to 52 weeks. In the analysis by Dr Vermeire, 48% of patients achieved a clinical response at week 16. Among the patients with a response at 16 weeks, the week 52 endpoints were better among those treated with 30 mg/day compared with 15 mg/day. The clinical takeaway from this analysis is that we should not give up on this therapy too early. Some patients may benefit from a longer treatment course. Among patients who take longer to respond to upadacitinib as maintenance therapy, a higher dose of 30 mg/day may be beneficial. The label for upadacitinib indicates that the 30-mg maintenance dose is appropriate in the setting of treatment-refractory or more severe disease. This indication applies to these patients for 2 reasons: previous anti-TNF therapy was unsuccessful, and the patients took longer to respond. Physicians should assess response to therapy early. If the patient does not achieve the preferred endpoint by the end of 8 weeks—and if the disease is not worsening—it may be appropriate to continue treatment for an additional 8 weeks. When transitioning to maintenance therapy, the higher dose of 30 mg/day should be used.

Ozanimod

Ozanimod is the first S1P receptor modulator approved by the FDA for the treatment of moderately to severely active UC. This drug targets S1P1 and S1P5. Ozanimod is also approved for the treatment of relapsing multiple sclerosis. An analysis from the phase 3 True North study showed that ozanimod was associated with a rapid response.[14,15] Treatment with ozanimod significantly improved symptomatic clinical response as early as week 2 compared with placebo.

This improvement strengthened and continued through week 10 of induction therapy. Notably, ozanimod was superior to placebo in patients with or without prior exposure to anti-TNF therapy. It is also notable that this supports the understanding of rapid cellular turnover in active inflammatory bowel disease, and that inhibiting cellular trafficking can have a rapid effect on symptoms.

There has been ongoing interest in objective measures of disease control in both clinical trials and clinical practice to confirm efficacy of therapy and to predict durability of treatment. A post hoc analysis of the True North study explored predicted outcomes based on mucosal healing among patients who responded to ozanimod.[16] Mucosal healing was defined using a stringent definition: a Mayo endoscopic score of 1 or 0 without friability and a histologic Geboes score of less than 2.0. The patients who received ozanimod and achieved this definition of mucosal healing by week 10 had improved clinical, endoscopic, and histologic outcomes at week 52. It is intuitive to think that patients who have a rapid healing of their bowel are likely to do better after a year. However, it is of great interest to inform the timing of assessment of patients, as well as to have information that we can provide to patients about disease stability and control throughout the coming year. One of the greatest messages we can provide to patients is that they will do well throughout the next year and will not become sicker. In practice, I routinely assess calprotectin as early as week 6. This study suggests that results from a calprotectin test at week 10 or an endoscopy with biopsies at week 10 will inform the likelihood that the patient will stay well through the rest of the year. Of course, negative results from the tests do not indicate that treatment will have no benefit. But a patient who achieves this level of response quickly will do very well.

As highlighted by the previous discussion of upadacitinib, extended therapy, delayed response, and delayed remission are of great interest in the setting of UC. Similarly, a post hoc analysis of the True North study examined extended therapy for patients with a delayed response to ozanimod.[17] The analysis found that patients who did not achieve a clinical response after the primary endpoint of 10 weeks benefited from an additional 5 or 10 weeks of ozanimod therapy. The rates of symptomatic clinical response were 44% after 5 weeks and 48.7% after 10 weeks. These findings suggest that patients who are not in remission by the end of 10 weeks, but who have not deteriorated, may benefit from ongoing use of ozanimod for a longer period of time. A separate analysis found that once a patient responds, even if the response was delayed, the likelihood of long-term benefit is equivalent to that of patients who responded early.[18] This finding is important for clinical practice, as it can help inform the decision to change or continue therapy. It is necessary to monitor patients to know whether longer-term induction might be necessary. This analysis provides reassurance that once a patient's disease is controlled, it is likely to remain under control for the next year.

A common question posed by patients is when they can stop therapy. The standard practice in inflammatory bowel disease is that continual maintenance therapy is needed in most patients to prevent relapse. Occasionally, patients must discontinue therapy because of factors such as intolerance, adverse events, insurance issues, and nonadherence. An analysis of the True North study examined patients with a clinical response to ozanimod at the end of induction week 10, who were then randomly assigned to placebo and developed relapsed disease.[19] These patients were offered treatment with open-label ozanimod. After re-initiation of ozanimod, the rate of symptomatic response was 55.8% at 5 weeks and 58.4% at 10 weeks. This finding is reassuring. It is notable, however, that there was still a percentage of patients who could not be recaptured. Therefore, it should not be misconstrued that patients can routinely discontinue therapy. More research is needed to identify patients who are candidates for a safe deintensification or de-escalation strategy.

The S1P receptor modulators are known to also have a specific receptor that is expressed and affects cardiac conduction. Ozanimod and etrasimod, a S1P receptor modulator in development, do not specifically target S1P3, but overlap of some targets is known to occur. Therefore, these therapies are titrated during induction to avoid asymptomatic bradycardia. A study by Dr Millie Long and colleagues evaluated the long-term cardiac safety of ozanimod in trials that enrolled patients with UC and relapsing multiple sclerosis.[20] The study confirmed the expected long-term cardiac safety profile, with a low incidence of asymptomatic bradycardia. This finding is expected based on the understanding of how ozanimod works. A reminder for clinicians is that patients with type 2 heart block should not receive ozanimod. However, other cardiovascular diseases are not a contraindication to the use of this therapy. This study provides reassurance that ozanimod is a good treatment option for patients. Unlike the JAK inhibitors, ozanimod can be prescribed before the use of an anti-TNF therapy and can therefore be administered earlier in the treatment course.

Etrasimod

Etrasimod is an S1P1, S1P4, and S1P5 receptor modulator. Dr William Sandborn and colleagues presented results of the phase 3 ELEVATE trial, in which patients with moderately to severely active UC were randomly assigned to etrasimod or placebo in a treat through design.[21] The patients received treatment during a 12-week induction period followed by a 40-week subsequent maintenance period. The "treat through" design differs from the usual randomized study design, in which patients who respond during induction therapy undergo a second

randomization to the drug or placebo during the maintenance period. With the "treat through" design, patients remain in their original randomized treatment arm from induction through maintenance. The design allows for an open-label extension for patients who do not respond or who lose response to treatment. In both the induction and maintenance phases of this study, etrasimod at 2 mg daily was superior to placebo in achieving clinical, endoscopic, symptomatic, and endo-histologic endpoints. In addition, there were no new safety findings for etrasimod, which was well tolerated. Etrasimod is undergoing further development.

Deucravacitinib

Deucravacitinib is a selective JAK inhibitor of tyrosine kinase 2. This agent is another novel, oral therapy that has multiple effects, including inhibition of IL-12 and IL-23, and has been shown to be quite effective in psoriasis.[22] This is a phase 2 trial that randomly assigned patients with moderately to severely active UC to deucravacitinib or placebo.[23] The trial did not meet its primary or secondary efficacy endpoints at week 12. The primary endpoint of clinical remission was 14.8% with deucravacitinib vs 16.3% with placebo (P=.59). The placebo response rates were higher than expected. In patients with prior exposure to biologic therapy, the response rates were numerically higher with deucravacitinib compared with placebo. Treatment with deucravacitinib led to an important decrease in fecal calprotectin and fecal lactoferrin compared with placebo. Overall, however, the results of this study were negative. The safety of deucravacitinib in this phase 2 trial was similar to that seen with psoriasis.[22] The investigators proposed that the high response rates seen with placebo were attributable to exposure to concomitant therapy. Further study with higher doses of deucravacitinib are underway.[24]

Disclosure

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