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A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis From the 17th Congress of the European Crohn's and Colitis Organisation

A Review of Selected Presentations From the 17th Congress of ECCO • February 16-19, 2022

Special Reporting on:

- Rapidity of Ozanimod-Induced Symptomatic Response and Remission in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Induction Period of True North
- 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
- Ozanimod Is an Efficacious Oral Therapy After 5-ASA Failure in Immunomodulator- and Biologic-Naive Patients With Ulcerative Colitis: Post Hoc Analysis From True North
- The Effects of Maintenance Therapy With Upadacitinib on Abdominal Pain, Bowel Urgency, and Fatigue in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 3 U-ACHIEVE Maintenance Results
- Long-Term Use of Ozanimod in Patients With Moderately to Severely Active Ulcerative Colitis
- Efficacy and Safety of Mirikizumab as Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 LUCENT-1 Study
- Long-Term Cardiac Safety of Ozanimod in a Phase 3 Clinical Program of Ulcerative Colitis and Relapsing Multiple Sclerosis
- Efficacy and Safety of Combination Induction Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis: Results Through Week 12 of a Phase 2a Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter, Proof-of-Concept Study
- Early Mucosal Healing at Week 10 With Ozanimod Predicts Clinical Outcomes at Week 52: Post Hoc Analysis of the Phase 3 True North Clinical Trial
- The Efficacy and Safety of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 2b QUASAR Study Results Through Week 12

PLUS Meeting Abstract Summaries

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Rapidity of Ozanimod-Induced Symptomatic Response and Remission in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Induction Period of True North

Ozanimod is an oral immunomodulatory agent that acts as a selective sphingosine-1-phosphate (S1P) receptor agonist. The multicenter, double-blind phase 3 True North trial evaluated ozanimod as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis.[1,2] During the 10-week induction period, patients in cohort 1 were randomly assigned in a 2:1 ratio to receive daily ozanimod hydrochloride (1 mg, equivalent to 0.92 mg of ozanimod) or placebo. Patients in cohort 2 received open-label ozanimod hydrochloride (1 mg). After 10 weeks, patients who demonstrated a clinical response to ozanimod were randomly assigned in a double-blind manner to receive ozanimod or placebo during the 42 weeks of the maintenance period. The primary endpoint was the proportion of patients with clinical remission, based on the 3-component Mayo score.[3]

To assess induction therapy, the True North trial randomly assigned 429 patients to ozanimod and 216 to placebo in cohort 1. In cohort 2, open-label ozanimod was administered to 367 patients. The maintenance period of the trial included 457 patients. The study demonstrated a significant increase in the incidence of clinical remission with ozanimod vs placebo, during both induction (18.4% vs 6.0%; *P*<.001) and maintenance (37.0% vs 18.5%; *P*<.001).[1] Treatment with ozanimod also yielded a greater proportion of patients with a clinical response compared with placebo, during both induction (47.8% vs 25.9%; *P*<.001) and maintenance (60.0% vs 41.0%; *P*<.001).

Britta Siegmund, MD, presented an analysis of the True North trial that evaluated the rapidity of symptomatic response and remission among patients who received ozanimod during the 10-week induction period.[2] A symptomatic response was defined as a decrease in the adapted partial Mayo score of at least 1 point and at least 30% from baseline, as well as a decrease of at least 1 point from baseline in the rectal bleeding subscore or an absolute rectal bleeding subscore of 1 or less. Symptomatic remission was defined as a rectal bleeding subscore of 0 and a stool frequency subscore of 1 point or less, as well as a decrease from baseline of 1 or more points.

The patients' baseline characteristics were generally well balanced among the 3 cohorts. The patients' mean age was 42 years, and their mean body mass index (BMI) was 25 to 26. The mean total Mayo score was approximately 9±1.5, and the mean partial Mayo score was approximately 6.1±1.2. Across the 3 cohorts, the proportion of patients with a rectal bleeding subscore of 2 or 3 ranged from 92% to 96%, and the proportion of patients with a stool frequency subscore of 2 or 3 ranged from 42% to 47%. Prior use of anti–tumor necrosis factor (TNF) agents was reported in 30% of patients in cohort 1 and 42% in cohort 2.

A first symptomatic response to treatment with ozanimod vs placebo was evident after 2 weeks of induction therapy, in both the overall study population (difference, 9.6%; Figure 1) and among patients without prior exposure to anti-TNF therapy (difference, 9.4%). Among patients with prior anti-TNF treatment, the first response to induction therapy was observed at 4 weeks (difference, 15.8%). Symptomatic remission was observed with ozanimod vs placebo at week 5 in the overall study population (difference, 8.6%; Figure 2), at week 4 in patients without prior exposure to anti-TNF therapy (difference, 9.4%), and at week 8 in patients with prior exposure to anti-TNF therapy (difference, 11.7%).

The investigators concluded that

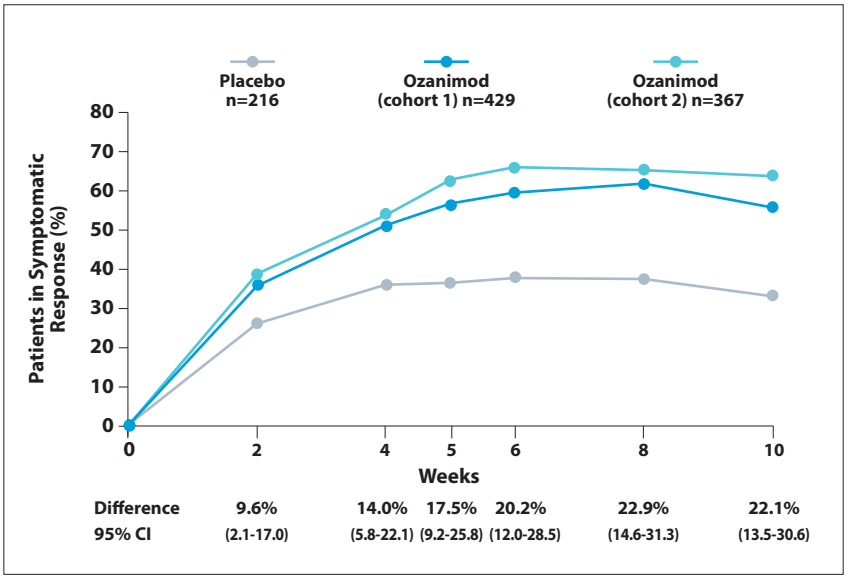

Figure 1. Symptomatic response in patients with moderately to severely active ulcerative colitis during induction treatment with ozanimod in the phase 3 True North trial. Adapted from Siegmund B et al. ECCO abstract DOP43. *J Crohns Colitis.* 2022;16(suppl 1).[2]

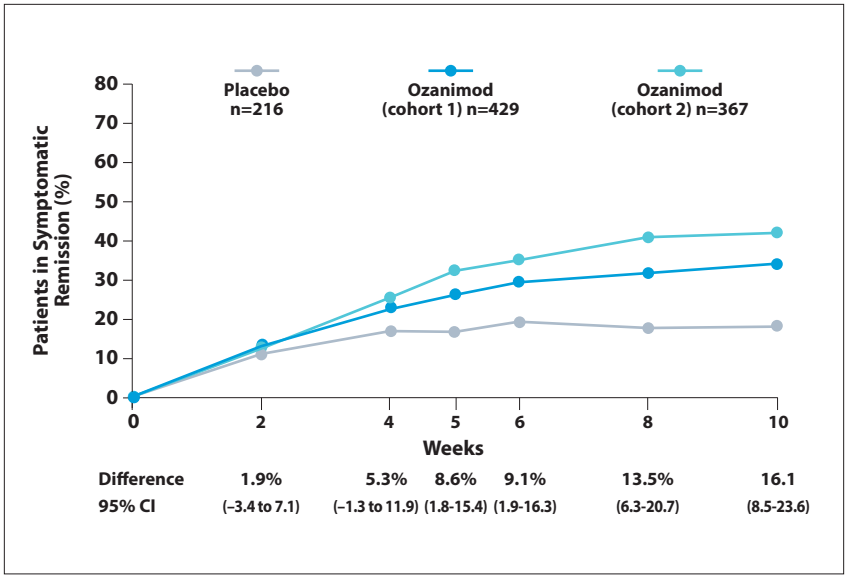

Figure 2. Symptomatic remission in patients with moderately to severely active ulcerative colitis during induction treatment with ozanimod in the phase 3 True North trial. Adapted from Siegmund B et al. ECCO abstract DOP43. *J Crohns Colitis*. 2022;16(suppl 1).[2]

treatment with ozanimod improved symptomatic response compared with placebo as early as 2 weeks after the initiation of treatment. Symptomatic remission was seen with ozanimod as early as 5 weeks after treatment began. For patients who were naive to TNF inhibitors, ozanimod led to a significant improvement in symptomatic response in as early as 2 weeks. This duration increased to 4 weeks among patients previously treated with TNF inhibitors. For symptomatic remission, ozanimod was associated with significant improvement as early as 4 weeks for patients naive to TNF inhibitors and as early as 8 weeks for those previously treated with TNF inhibitors.

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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

Phase 2b and phase 3 studies have demonstrated the safety and efficacy of upadacitinib (45 mg) when administered daily for 8 weeks as induction treatment for patients with moderately to severely active ulcerative colitis.[1-3] A study evaluated the safety and efficacy of 16 weeks of induction therapy with daily upadacitinib at 45 mg, followed by 52 weeks of maintenance therapy with daily upadacitinib administered at 15 mg or 30 mg.[4] The patient population consisted of 125 patients with ulcerative colitis without a clinical response after 8 weeks of induction therapy with upadacitinib in the U-ACHIEVE study. Clinical response was defined as a decrease in the adapted Mayo score of 2 or more points and 30% from baseline, plus a

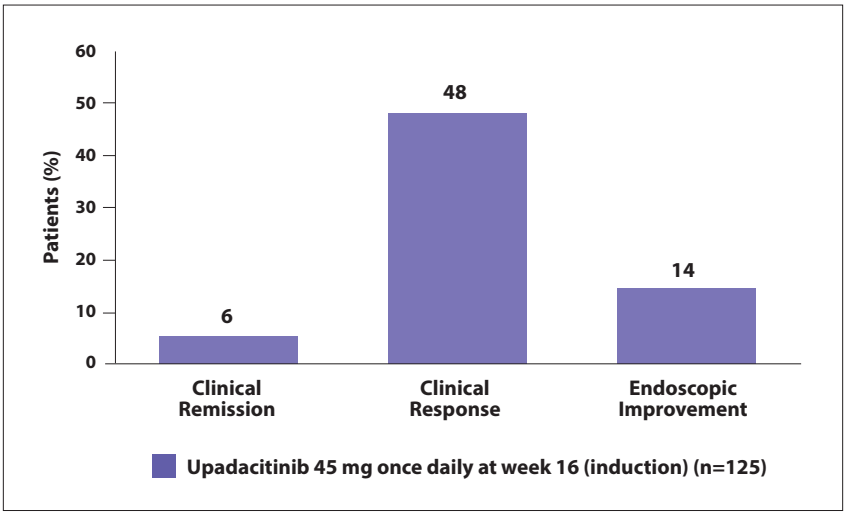

Figure 3. Efficacy after 16 weeks of extended induction treatment with upadacitinib at 45 mg/day among patients with ulcerative colitis without an initial clinical response in the U-ACHIEVE trial. Adapted from Vermeire S et al. ECCO abstract DOP41. *J Crohns Colitis*. 2022;16(suppl 1).[4]

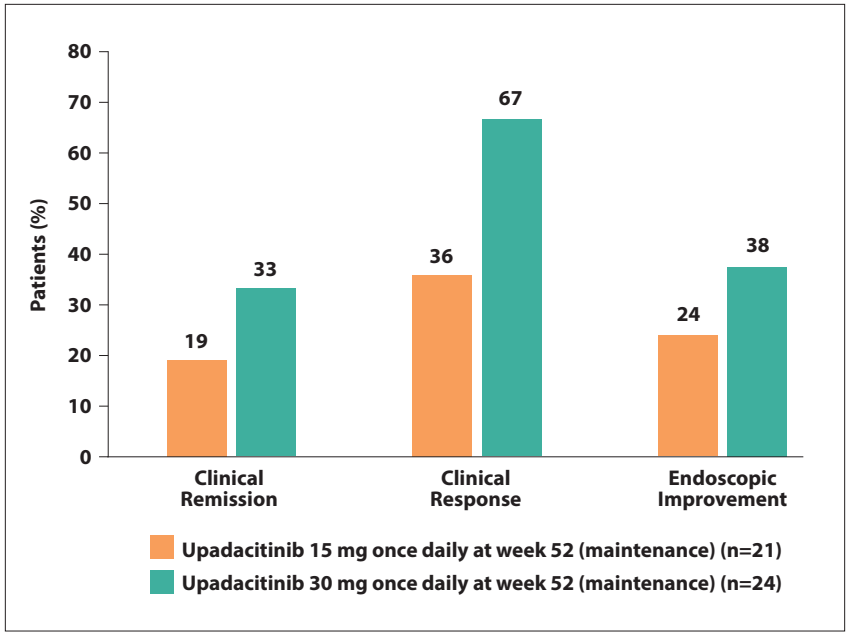

Figure 4. Efficacy after 52 weeks of maintenance treatment with upadacitinib at 15 mg/day or 30 mg/day among patients with ulcerative colitis without an initial clinical response in the U-ACHIEVE trial. Adapted from Vermeire S et al. ECCO abstract DOP41. *J Crohns Colitis*. 2022;16(suppl 1).[4]

decrease of at least 1 point in the rectal bleeding score or an absolute rectal bleeding score of 1 or lower. A response to extended induction therapy was reported in 73 of 125 patients (58%), and 45 of these patients completed the U-ACHIEVE maintenance study.

Among the 125 patients who entered the study's extended treatment period, the mean age was 43.1 years, and 27% were female. The patients had a mean BMI of 24.3±4.06 kg/m^2, a mean disease duration of 6.71±5.92 years, and a mean adapted Mayo score of 6.96±1.14. Among 125 patients who received 8 additional weeks of induction therapy with upadacitinib at 45 mg, 48.3% achieved a clinical response and were randomly assigned to maintenance therapy with daily upadacitinib administered at 15 mg or 30 mg (Figure 3). After 52 weeks of maintenance therapy, efficacy outcomes were superior with the higher dose of upadacitinib. The rate of clinical remission was 19% with 15 mg/day vs 33% with 30 mg/day (Figure 4). The rate of clinical response was 36% vs 67%, respectively, and the rate of endoscopic improvement was 24% vs 38%.

The rates of adverse events (AEs) were similar for both doses of maintenance upadacitinib. Similar rates were reported for AEs of special interest, such as anemia (5.7% with 15 mg/day vs 7.5% with 30 mg/day), elevated creatine phosphokinase (5.7% vs 5.0%), and serious infection (2.9% vs 5.0%). AEs of special interest that were observed only among the patients who received the higher dose of upadacitinib included hepatic disorder (7.5%), herpes zoster (5.0%), neutropenia (5.0%), adjudicated major adverse cardiovascular events (2.5%), and nonmelanoma skin cancer (2.5%).

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Ozanimod Is an Efficacious Oral Therapy After 5-ASA Failure in Immunomodulator- and Biologic-Naive Patients With Ulcerative Colitis: Post Hoc Analysis From True North

A post hoc analysis of data from the phase 3 True North trial assessed the efficacy of 10 weeks of ozanimod induction therapy, with or without concomitant corticosteroid treatment.[1,2] The patients had received prior treatment with 5-aminosalicylic acid, but not with immunomodulators or biologic therapies. Bruce Sands, MD, presented the results.[1] Among 464 enrolled patients, 101 received placebo and 205 received ozanimod in cohort 1, while 158 received open-label ozanimod in cohort 2.

Among all patients in the analysis, clinical remission at week 10 was reported in 23.4% of cohort 1, 30.4% of cohort 2, and 8.9% of the placebo arm (*P*=.002 vs cohort 1). A clinical response occurred in 53.7% of cohort 1, 62.7% of cohort 2, and 30.7% of the placebo arm (*P*=.0002 vs cohort 1). Endoscopic improvement was reported in 35.6% of cohort 1, 38% of cohort 2, and 14.9% of the placebo arm (*P*=.0002 vs cohort 1). Mucosal healing occurred in 18% of cohort 1, 14.6% of cohort 2, and 5.0% of the placebo arm (*P*=.002 vs cohort 1).

At week 10, in cohort 1, the

rate of clinical remission was 19.0% with ozanimod vs 5.0% with placebo (*P*=.142) among the patients receiving concomitant corticosteroids. Among patients who were not receiving corticosteroids, clinical remission was reported in 24.5% of the ozanimod arm vs 9.9% of the placebo arm (*P*=.007). The rate of clinical response was 59.5% with ozanimod vs 30.0% with placebo in patients who concomitantly used corticosteroids (*P*=.030), and 52.1% vs 30.9% (*P*=.002) in those who did not.

In cohort 1, the rate of endoscopic improvement was 35.7% with ozanimod vs 15% with placebo (*P*=.093) in patients receiving corticosteroids and 35.6% vs 14.8% (*P*=.001) in those who were not. Rates of mucosal healing were 19% with ozanimod vs 5.0% with placebo (*P*=.142) in those receiving corticosteroids and 17.8% vs 4.9% (*P*=.006) in those who were not.

Treatment-emergent AEs did not differ according to the use of corticosteroids. In cohort 1, at least 1 treatment-emergent AE occurred in 47.6% of the patients receiving corticosteroids vs 31.3% of those who were not. In the placebo arm, these rates were 30% vs 28.4%, respectively.

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The Effects of Maintenance Therapy With Upadacitinib on Abdominal Pain, Bowel Urgency, and Fatigue in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 3 U-ACHIEVE Maintenance Results

Upadacitinib is a reversible, selective Janus kinase (JAK) inhibitor.[1] In the phase 3 U-ACHIEVE and U-ACCOMPLISH trials, induction therapy with upadacitinib was superior to placebo in patients with moderately to severely active ulcerative colitis who required treatment after previous therapy.[2,3] Improvements were reported in symptoms such as abdominal pain, bowel urgency, and fatigue, which can be debilitating to these patients.[4]

Patients who demonstrated a clinical response during the 8-week induction period with daily upadacitinib (45 mg) were enrolled in the U-ACHIEVE maintenance trial. Silvio Danese, MD, PhD, presented results for this cohort.[5] This study randomly assigned 451 patients to receive upadacitinib at 15 mg, upadacitinib at 30 mg, or placebo, in a double-blind manner. Patient-reported outcomes of abdominal pain and bowel urgency were assessed during maintenance treatment. The Functional Assessment of Chronic Illness

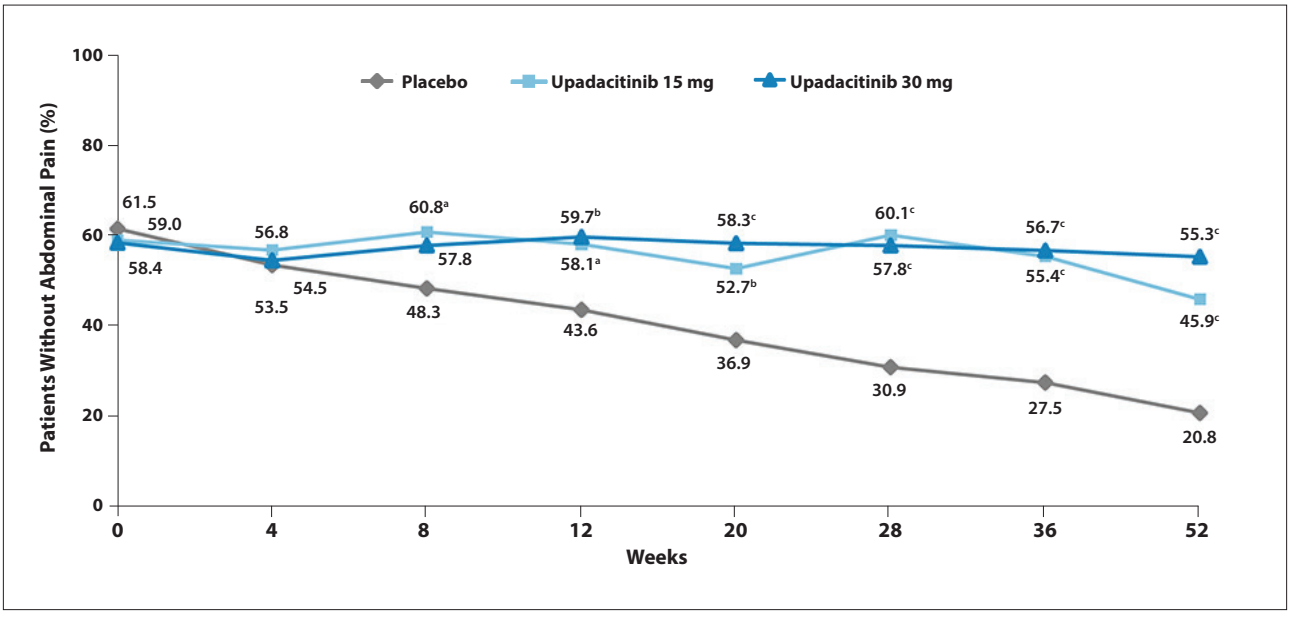

Figure 5. Abdominal pain among patients with moderately to severely active ulcerative colitis in the U-ACHIEVE maintenance trial, which evaluated upadacitinib at 15 mg or 30 mg. [a]*P*<.05 for upadacitinib vs placebo. [b]*P*<.01 for upadacitinib vs placebo. [c]*P*<.001 for upadacitinib vs placebo. Adapted from Danese S et al. ECCO abstract OP08. *J Crohns Colitis*. 2022;16(suppl 1).[5]

Therapy Fatigue (FACIT-F) instrument was used to measure fatigue. A change of 5 or more points from baseline in the FACIT-F score was considered a meaningful within-person change, and an increase of 40 or more points was considered normalization of fatigue.

By week 12 of the maintenance period, the proportion of patients without abdominal pain was 59.7% with upadacitinib at 30 mg (P<.01 vs placebo), 58.1% with upadacitinib at 15 mg (P<.05 vs placebo), and 43.6% with placebo (Figure 5). The proportion of patients without abdominal pain remained fairly constant throughout the maintenance period for both upadacitinib cohorts. In contrast, the proportion of patients without abdominal pain consistently decreased in the placebo group. At week 52, the proportion of patients without abdominal pain was 55.3% with the higher upadacitinib dose, 45.9% with the lower dose, and 20.8% with placebo (P<.001). Similar outcomes for the 3 groups were observed in terms of bowel urgency. The proportion of patients with no bowel urgency from week 8 through week 52 fluctuated between 63.6% and 68.8% in the 30-mg upadacitinib group and between 56.1% and 64.3% in the 15-mg upadacitinib group. In contrast, the proportion of patients in the placebo group with no bowel urgency consistently decreased from 49.7% at week 8 to 17.4% at week 52. At week 52 of the maintenance period, the proportion of patients with meaningful within-person change as measured by the FACIT-F score was 58.8% with the higher dose of upadacitinib, 55.4% with the lower dose, and 35.1% with placebo (P<.001). Normalized fatigue scores were reported in 55.7%, 52.0%, and 35.7%, respectively.

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Long-Term Use of Ozanimod in Patients With Moderately to Severely Active Ulcerative Colitis

The phase 3 True North open-label extension study evaluated the long-term safety and efficacy of ozanimod in patients with moderately to severely active ulcerative colitis.[1,2] Ozanimod hydrochloride was administered at 1 mg/day. Efficacy endpoints, including clinical remission, clinical response, endoscopic improvement, and corticosteroid-free remission, were evaluated at 46, 94, and 142 weeks. Efficacy endpoints at 142 weeks were not evaluated for the cohort of patients with a clinical response at baseline because too few of these patients were available for analysis at the time of data cutoff. Data from the trial were analyzed in

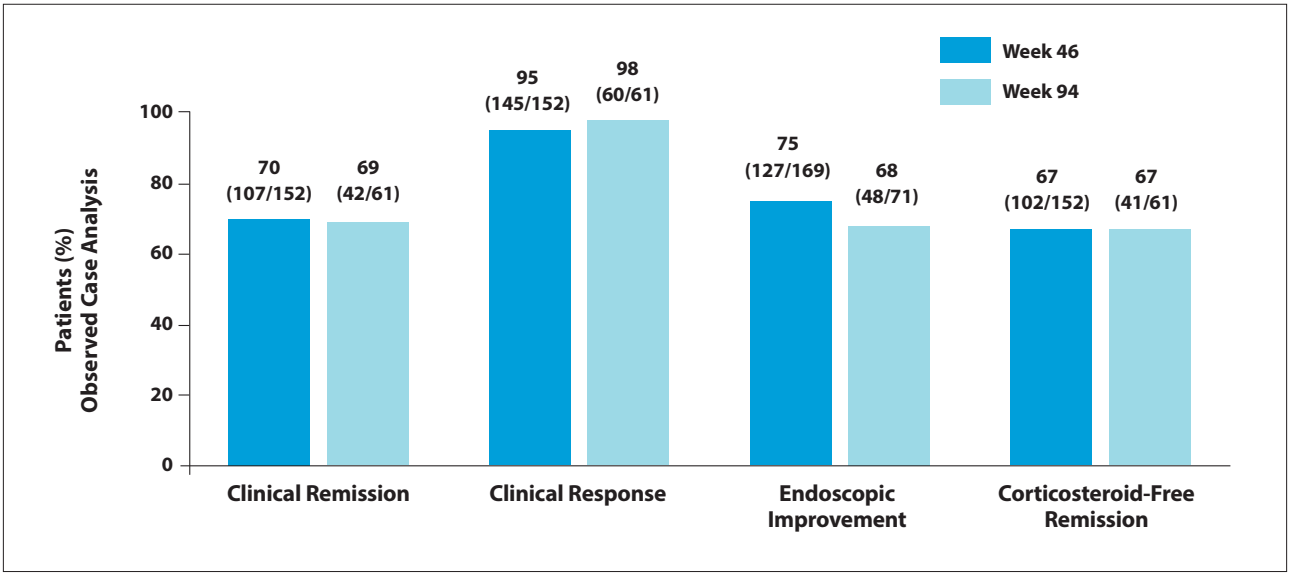

Figure 6. Efficacy of ozanimod in the phase 3 True North open-label extension study in patients with moderately to severely active ulcerative colitis who had a clinical response at study entry. Data were not included for week 142 due to insufficient patient numbers at data cutoff. Adapted from Danese S et al. ECCO abstract DOP44. *J Crohns Colitis*. 2022;16(suppl 1).[1]

the intention-to-treat population by means of observed cases (using data only from patients remaining in the trial) or by nonresponder imputation (including data from patients who had withdrawn from the trial). The open-label extension study enrolled 823 patients, including 261 patients who entered the extension study with a clinical response.[1] The 823 patients represented 1201 years of exposure to ozanimod, with a mean ozanimod exposure during the extension study of 1.5 years per patient. Completion rates were 64% at week 46, 34% at week 94, and 14% at week 142. Among the 358 patients who withdrew from the study, the most common primary reason was lack of efficacy (21%).

In the overall study population, the patients' mean age was 41.7 years, and 59% were male. The mean BMI was 25.38±5.4 kg/m^2. At screening, 32% of patients were receiving corticosteroids. The most common prior medications included oral 5-aminosalicylate (97.7%), corticosteroids (75.7%), and immunomodulators (42.0%).

Based on an analysis of observed cases, efficacy rates were maintained at week 46, week 94, and week 142.[1] Among all patients who enrolled in the extension study, clinical remission rates at 46 weeks, 94 weeks, and 142 weeks ranged from 45% to 51%. Clinical response rates ranged from 80% to 86%. Rates of endoscopic improvement ranged from 49% to 57%. The rates of corticosteroid-free remission ranged from 40% to 50%.

Among the 261 patients with a clinical response at study entry, clinical remission was reported in 70% at week 46 and 69% at week 94 (Figure 6). Rates of clinical response were 95% at week 46 and 98% at week 94. Endoscopic improvement was reported in 75% at week 46 and 68% at week 94. Corticosteroid-free remission occurred in 67% of patients at both time points. Similar trends were observed when using nonresponder imputation analysis, which showed a clinical response rate at week 94 of 28% in the overall study population and 55% in the cohort of patients with a clinical response at baseline.

Safety data were available from phase 2 and 3 studies of ozanimod in 1158 patients with ulcerative colitis, representing 2108 patient-years.[1] No new safety signals were observed with long-term use in this setting. The most common treatment-emergent AEs consisted of lymphopenia (10.3%), anemia (7.9%), and nasopharyngitis (7.5%). The most common serious treatment-emergent AEs were worsening of ulcerative colitis (3.9%), anemia (0.9%), and appendicitis (0.5%). Treatment-emergent AEs led to discontinuation of ozanimod in 8% of patients.

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Efficacy and Safety of Mirikizumab as Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 LUCENT-1 Study

Mirikizumab is a humanized, immunoglobulin G4 antibody that binds to the p19 subunit of interleukin (IL) 23, thereby inhibiting a known proinflammatory pathway. In a randomized phase 2 study of patients with moderately to severely active ulcerative colitis, the rate of clinical response was significantly greater with mirikizumab compared with placebo.[1] The multicenter, parallel-arm phase 3 LUCENT-1 trial compared mirikizumab vs placebo in patients with moderately to severely active ulcerative colitis.[2] The trial enrolled patients ages 18 to 80 years, with a modified Mayo score of 4 to 9 and an endoscopic subscore of 2 or higher. The patients had experienced an inadequate response, loss of response, or were intolerant to corticosteroids or immunomodulator therapy, biologic therapy, or a JAK inhibitor. The stratification factors included failure of biologic therapy, baseline corticosteroid use, baseline disease activity, and geographic region. The patients were randomly assigned 3:1 to receive mirikizumab (300 mg) or placebo, administered every 4 weeks in a double-blind manner. The primary objective of the study was clinical remission at week 12 of induction, with clinical remission defined as a stool frequency of 0, or a value of 1 with at least a 1-point decrease from baseline; a rectal bleeding score of 0; and a Mayo endoscopic subscore of 0 or 1, excluding friability. A *P* value of .00125 was considered statistically significant.

The LUCENT-1 trial randomly assigned 868 patients to the mirikizumab arm and 294 to the placebo arm. The baseline characteristics were generally well balanced between the 2 arms. The patients' mean age was approximately 42 years, and 58% of patients were male. Based on the modified Mayo score, 47% of patients had moderately active ulcerative colitis and 53% had severely active disease. At baseline, treatment included corticosteroids in 39% of patients and immunomodulators in 24%. Prior unsuccessful treatments included biologic or tofacitinib therapy in 41% of patients and anti-TNF therapy in 35%.

After 12 weeks of induction treatment, the rate of clinical remission across the entire study population was

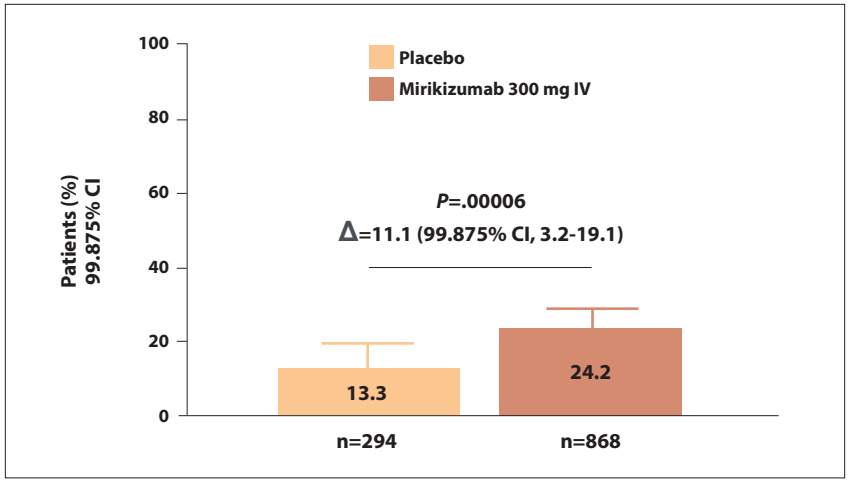

Figure 7. Clinical remission at week 12 among patients with moderately to severely active ulcerative colitis who received mirikizumab or placebo as induction therapy in the phase 3 LUCENT-1 study. IV, intravenous. Adapted from D'Haens G et al. ECCO abstract OP26. *J Crohns Colitis*. 2022;16(suppl 1).[2]

24.2% with mirikizumab vs 13.3% with placebo (*P*=.00006; Figure 7). Among patients without prior exposure to biologic therapy, the rate of clinical remission was 30.9% with mirikizumab vs 15.8% with placebo (*P*<.001). Among patients who had received unsuccessful biologic therapy, the rate of clinical remission was 15.2% vs 8.5%, respectively, a difference that did not reach statistical significance (*P*=.065). Mirikizumab led to a superior rate of clinical response at week 12 among the overall study population (63.5% vs 42.2%; *P*<.00001), among patients who had not received prior biologic therapy (70.1% vs 50.3%; *P*<.001), and among patients who had received prior biologic therapy (54.6% vs 29.7%; *P*<.001). In the overall study population, the rate of endoscopic remission was 36.3% with mirikizumab vs 21.1% with placebo (*P*<.00001), and the rate of histologic mucosal improvement was 27.1% vs 13.9%, respectively (*P*<.00001). The overall safety profile of mirikizumab was similar to that observed in prior studies, with rates of AEs that were comparable with or lower than those observed with placebo.

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

Modulators of S1P receptor activity may be associated with cardiovascular issues, including bradycardia and delayed atrioventricular conduction.[1] To evaluate the long-term cardiovascular risks associated with S1P receptor modulators, a retrospective study examined the impact of continuous ozanimod use on heart rate, blood pressure, and cardiovascular AEs in patients with ulcerative colitis or multiple sclerosis.[2-5] The patients with ulcerative colitis were drawn from the True North trial, and all received ozanimod at 0.92 mg/day.[4] Electrocardiograms (ECGs) were conducted at screening and on day 1, week 10, and week 52, and heart rate was monitored at every visit. Patients with multiple sclerosis had participated in either the SUNBEAM or the RADIANCE trial and had been randomly assigned to receive ozanimod at 0.46 mg/day or 0.92 mg/day.[2,3] In these studies, ECGs were conducted at screening, baseline, on day 15, and at the end of treatment. Heart rate was measured at baseline and then every 3 months until the end of treatment.

In the group of 230 patients with ulcerative colitis who received continuous ozanimod for both induction and maintenance, the mean change in heart rate was –1.0 beat per minute (Figure 8).[5] In the same population, systolic blood pressure increased by 5 mm Hg, and diastolic blood pressure increased by 2.2 mm Hg. In contrast, blood pressure values remained the same in patients in the placebo arm and in those who received ozanimod induction without maintenance therapy.

The overall incidence of cardiovascular AEs was low. Among 796 patients who received induction treatment with daily ozanimod, the most common cardiovascular disorders consisted of bradycardia (0.6%), palpitations (0.4%), and tachycardia (0.4%). Among the 230 patients who received daily ozanimod induction followed by maintenance therapy, the rate of bradycardia was 1.3%. Arrhythmia, chronic cardiac failure, coronary artery disease, and pericarditis were each observed in 0.4% of patients.

Among patients with ulcerative colitis, serious AEs included angina pectoris, coronary artery stenosis, pericarditis, and hypertensive crisis, each observed in 1 patient. Similarly, data from the pooled multiple sclerosis studies showed that no clinically significant

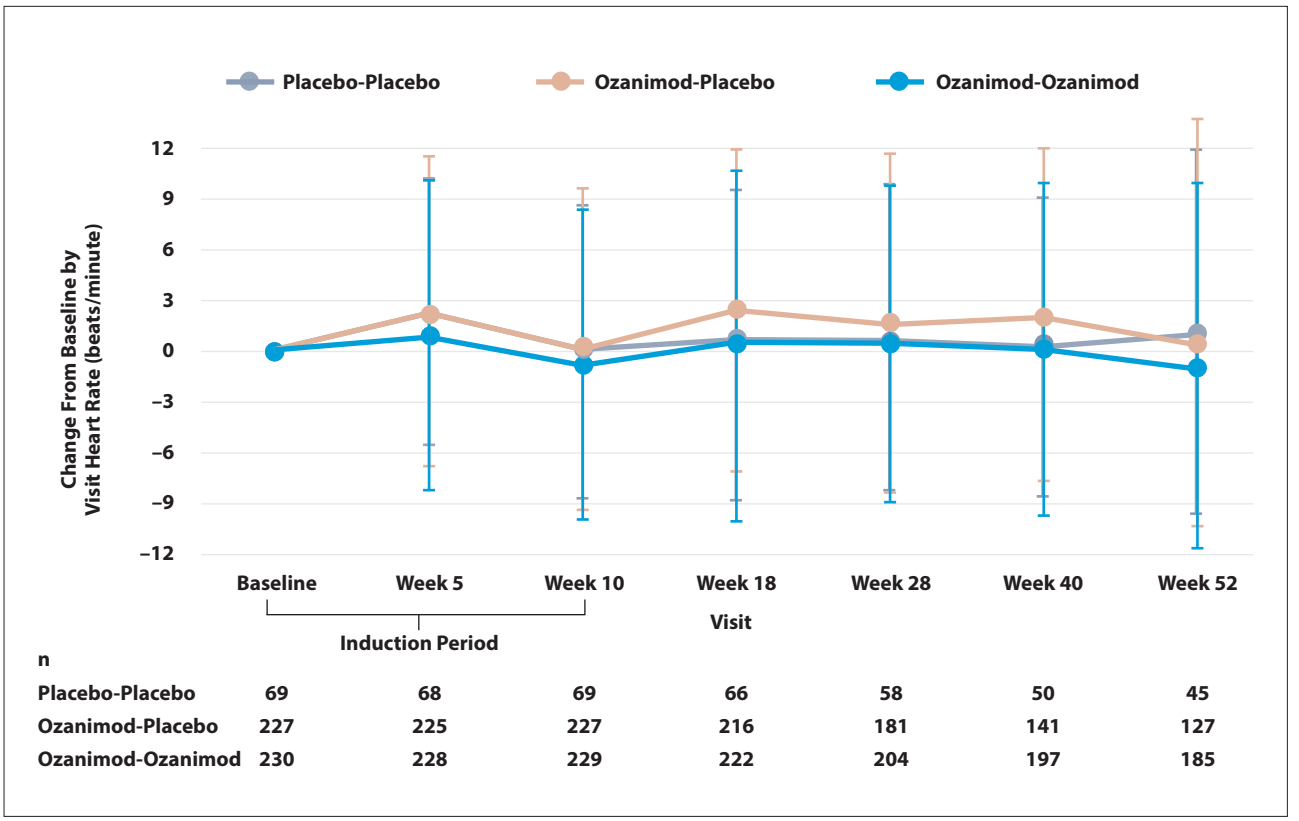

Figure 8. Impact of continuous treatment with ozanimod on heart rate in an analysis of patients with ulcerative colitis enrolled in the phase 3 True North trial. Adapted from Armuzzi A et al. ECCO abstract DOP45. *J Crohns Colitis*. 2022;16(suppl 1).[5]

changes occurred in heart rate or ECG. The incidence of treatment-emergent AEs was low, and only 2 of 882 patients with multiple sclerosis experienced a serious cardiac AE. In summary, data from phase 3 trials showed that long-term administration of ozanimod was associated with a manageable cardiac safety profile in patients with ulcerative colitis and multiple sclerosis.

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Efficacy and Safety of Combination Induction Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis: Results Through Week 12 of a Phase 2a Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter, Proof-of-Concept Study

Guselkumab is an antagonist of the p19 subunit of IL-23 that is approved to treat plaque psoriasis. Golimumab is an antagonist of TNFα and is approved for the treatment of ulcerative colitis.[1] The phase 2a VEGA study evaluated the safety and efficacy of induction therapy with guselkumab plus golimumab vs monotherapy with guselkumab or golimumab in adults with moderately to severely active ulcerative colitis.[2] The

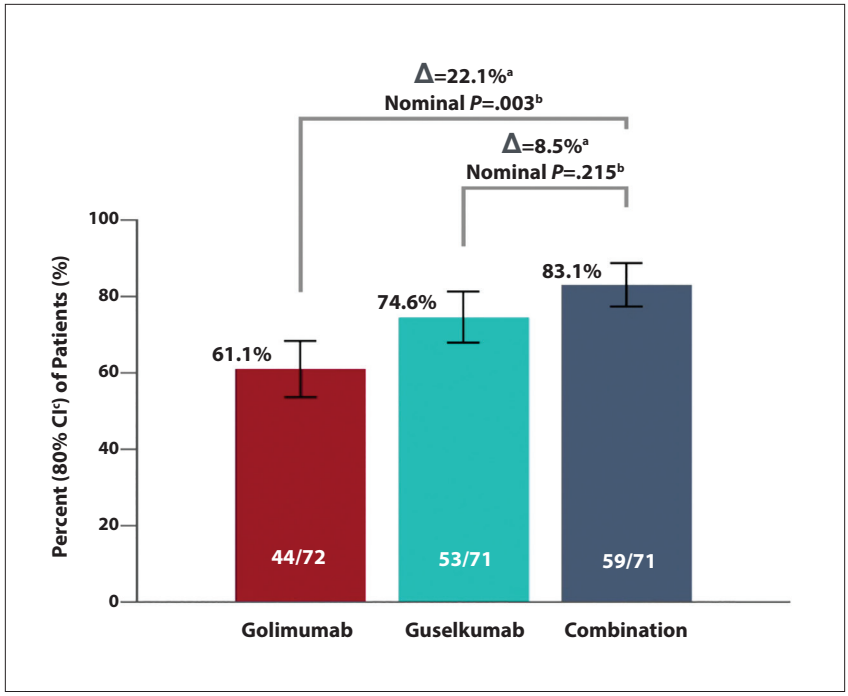

Figure 9. Clinical response among patients with moderately to severely active ulcerative colitis after 12 weeks of induction therapy in a phase 2a trial that evaluated golimumab monotherapy, guselkumab monotherapy, and the combination of golimumab and guselkumab. [a]The adjusted treatment difference between the combination therapy vs the monotherapy groups were based on the Wald statistics with the CMH weight. [b]The *P* value was based on the CMH chi-square text, stratified by the use of corticosteroids at baseline (yes vs no). [c]The 80% CIs for response rate were based on the Wald statistic. CMH, Cochran–Mantel–Haenszel Adapted from Sands BE et al. ECCO abstract OP36. *J Crohns Colitis*. 2022;16(suppl 1).[2]

trial enrolled patients with a Mayo score of 6 to 12 and an endoscopy subscore of 2 or lower according to central review. The patients had received prior therapy that was either intolerable or unsuccessful. The trial excluded patients previously treated with a TNFα antagonist.

Patients were randomly assigned into the 3 arms. In the golimumab monotherapy arm, this agent was administered at 200 mg subcutaneously at week 0, followed by 100 mg administered at weeks 2, 6, and 10. In the guselkumab monotherapy arm, treatment was administered at 200 mg intravenously at weeks 0, 4, and 8. For combination therapy, the 2 antibodies were administered in combination at the same doses and schedules. The induction phase for all 3 arms continued for 12 weeks. The primary endpoint was clinical response, defined as a decrease from baseline in the Mayo score of at least 30% and 3 points, with either a decrease in the rectal bleeding subscore of 1 or more or a rectal bleeding subscore of 0 or 1.

Among the entire study population of 214 patients, the mean age was 38.4 years, and 54.2% were male. The mean duration of ulcerative colitis was 4.9±4.9 years. The mean Mayo score was 8.8. The endoscopy subscore was moderate in 41% of patients and severe in 59%. Prior use of immunosuppressants was noted in 42% of patients, and 41% were using corticosteroid therapy at baseline.

After 12 weeks of induction therapy, the proportion of patients with a clinical response was 61.1% with golimumab monotherapy, 74.6% with guselkumab monotherapy, and 83.1% with the combination (Figure 9). The difference of 22.1% for the dual antibody therapy vs golimumab alone was statistically significant (*P*=.003). However, the 8.5% difference for the combination vs guselkumab was not significant (*P*=.215). Based on a Mayo score no greater than 2 and no individual subscore greater than 1, the rate of clinical remission was 22.2% with golimumab monotherapy, 21.1% with guselkumab monotherapy, and 36.6% with the combination (*P*=.058 vs golimumab alone; *P*=.041 vs guselkumab alone). Using a modified Mayo score, the rate of clinical remission was 25.0% with golimumab, 23.9% with guselkumab, and 46.5% with the antibody combination (*P*=.007 vs golimumab alone; *P*=.005 vs guselkumab alone). The rate of endoscopic improvement was significantly improved with the 2-antibody therapy compared with golimumab monotherapy (*P*=.003) or guselkumab monotherapy (*P*=.016). However, the rates of endoscopic normalization were not significantly different for either monotherapy treatment vs the antibody combination

The rates of AEs were comparable among the 3 treatment groups. AEs required discontinuation of the study treatment in 4.2% of the golimumab arm, 1.4% of the guselkumab arm, and 2.8% of the combination arm.

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Early Mucosal Healing at Week 10 With Ozanimod Predicts Clinical Outcomes at Week 52: Post Hoc Analysis of the Phase 3 True North Clinical Trial

The phase 3 True North trial compared ozanimod vs placebo among patients with moderately to severely active ulcerative colitis.[1] The trial included a 10-week induction phase followed by a maintenance phase that lasted 42 weeks. Treatment with ozanimod led to significant improvements in clinical, endoscopic, and histologic outcomes compared with placebo. Mucosal healing was defined as endoscopic improvement and histologic remission. Based on a treat-to-target strategy as outlined in the Selecting Therapeutic Targets in Inflammatory Bowel Disease consensus guidelines, mucosal healing is an important treatment target.[2] To determine the relationship between early mucosal healing after induction therapy and clinical outcomes after maintenance therapy, a post hoc analysis evaluated various efficacy outcomes at week 52 in patients who did or did not achieve mucosal healing at week 10 of induction therapy.[3]

In the True North trial, 230 patients received ozanimod during the induction and maintenance periods.[1] Among these patients, 44 (19.1%) achieved mucosal healing at week 10. The patients' mean age was 43 years, and 51% were male. The mean BMI was 26 kg/m^2. The mean time since the diagnosis of ulcerative colitis was 8.3 years. The mean total Mayo score was 8.9.

Among the 186 patients who had not achieved mucosal healing after 10 weeks of ozanimod induction therapy, 24.2% achieved mucosal healing by week 52.[3] Mucosal healing at week 10 was associated with a greater likelihood of clinical remission (47.7% vs 34.4%), corticosteroid-free remission (45.5% vs 28.5%), mucosal healing (52.3% vs 24.2%), endoscopic improvement (63.6% vs 41.4%), and histologic remission (56.8% vs 28.0%; Figure 10).[3] Among the patients who did not achieve mucosal healing at week 10 of induction therapy, the rate of mucosal healing was 25.8% in those without prior anti-TNF exposure vs 21.2% in those with prior anti-TNF exposure. Efficacy outcomes were improved to a greater degree among patients who had not received prior treatment with an anti-TNF agent.

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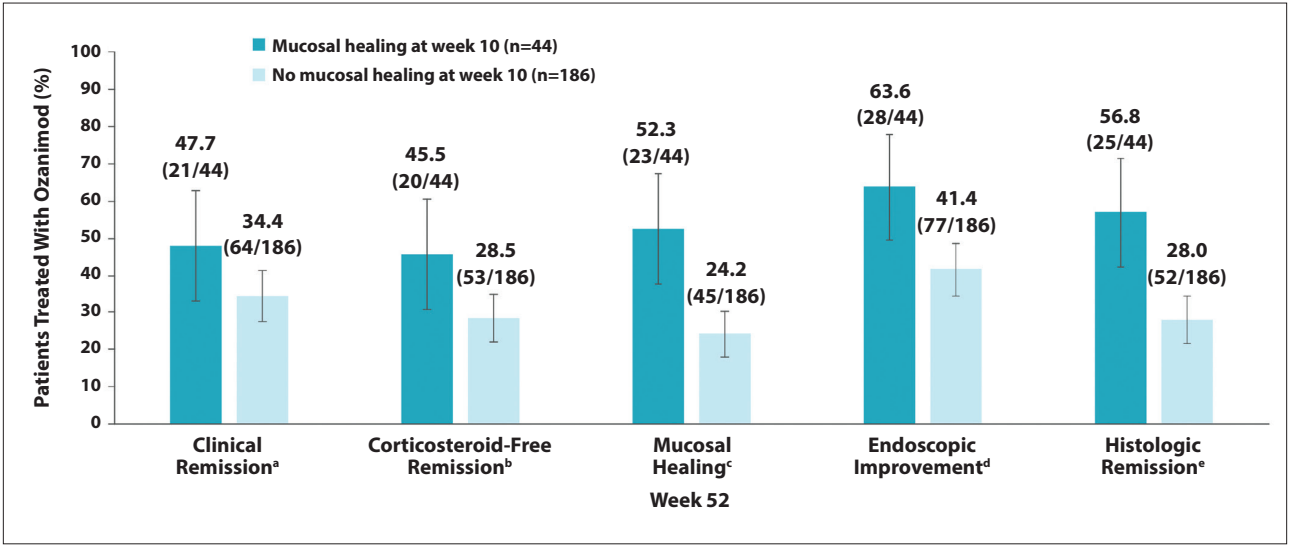

Figure 10. Efficacy according to mucosal healing at week 10 in an analysis of patients treated with ozanimod in the phase 3 True North trial. [a]Rectal bleeding score of 0, stool frequency subscore of ≤1 (plus a ≥1-point reduction from baseline), and a mucosal endoscopy subscore of ≤1, without friability. [b]Remission with no corticosteroid use for ≥12 weeks. [c]Endoscopic improvement plus histologic remission. [d]Mucosal endoscopy subscore of ≤1 without friability. [e]Defined as a Geboes score of <2.0 with absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue. Adapted from Reinisch W et al. ECCO abstract P431. *J Crohns Colitis*. 2022;16(suppl 1).[3]

The Efficacy and Safety of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 2b QUASAR Study Results Through Week 12

The randomized, double-blind phase 2b QUASAR Induction Study 1 evaluated the safety and efficacy of 12 weeks of guselkumab in patients with moderately to severely active ulcerative colitis.[1] The trial enrolled patients previously treated with conventional or advanced therapy that was intolerable or inadequate. Their Mayo rectal bleeding score was 1 or higher at baseline and their Mayo endoscopy subscore was at least 2, based on central review. The patients were randomly assigned to receive placebo, guselkumab at 200 mg every 4 weeks, or guselkumab at 400 mg every 4 weeks. The primary endpoint was the clinical response at week 12.

Among the entire study population of 313 patients, the median age was 41.6±14.40 years, and 59.1% were male. The mean duration of ulcerative colitis was 7.55±6.79 years. The mean Mayo score was 9.2±1.32, and the mean modified Mayo score was 7.0±1.0. Seventy percent of patients had a modified Mayo score of 7, 8, or 9, and 70% of patients had an endoscopy subscore of 3, indicating severe disease. Medications in use at baseline included oral aminosalicylates (77.3%), oral corticosteroids (39.6%), and immunosuppressants (21.7%), and 23.3% of patients were intolerant to 2 or more classes of advanced therapy.

Nine patients (2.9%) discontinued treatment, most commonly owing to study withdrawal (1.0%) or worsening ulcerative colitis (1.0%). Results with the 2 doses of guselkumab were generally comparable. At week 12 of induction, the proportion of patients with a clinical response was 27.6% with placebo, 61.4% with the lower dose of guselkumab, and 60.7% with the higher dose of guselkumab (*P*<.001 for both; Figure 11). Rates of clinical remission were 9.5% with placebo vs 25.7% with the lower dose of guselkumab and 25.2% with the higher dose of guselkumab (*P*<.05 for both). The rates of symptomatic remission were 50.5% with the lower dose of guselkumab, 47.7% with the higher dose, and 20% with placebo (*P*<.001 for both). The rate of endoscopic improvement was 30.7% (*P*<.05 vs placebo), 30.8% (*P*<.001 vs placebo), and 12.4%, respectively. The rate of histo-endoscopic improvement at week 12 was 19.8% (*P*<.05 vs placebo) with the lower dose of guselkumab, 27.1% (*P*<.001 vs placebo) with the higher dose, and 8.6% with placebo. The rate of endoscopic normalization was also significantly worse with placebo (6.7%) compared with the lower dose of guselkumab (19.8%; *P*<.05 vs placebo). The comparison did not reach statistical significance with the higher dose of guselkumab (14.0%; *P*>.05 vs placebo).

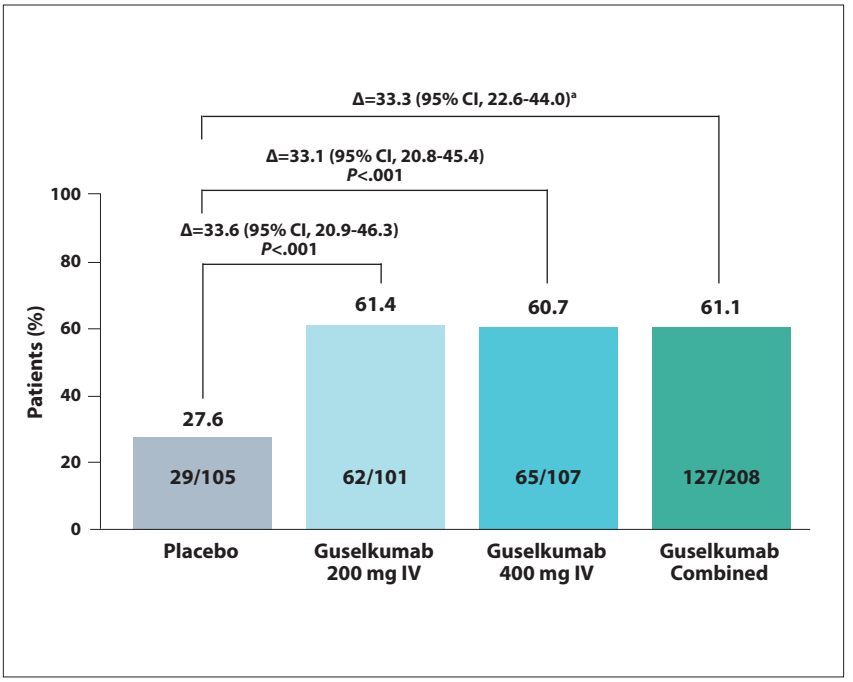

Figure 11. Clinical response at week 12 in the phase 2b QUASAR study, which evaluated induction therapy with guselkumab in patients with moderately to severely active ulcerative colitis. [a]Nominal *P* value <.001. IV, intravenous. Adapted from Dignass A et al. ECCO abstract OP32. *J Crohns Colitis*. 2022;16(suppl 1).[1]

Safety results were generally consistent with observations from previous studies in approved indications. The rate of serious AEs was 1% in the guselkumab arms vs 5.7% in the placebo arm. AEs required treatment discontinuation in 0.5% vs 1.9%, respectively. The rate of infection was 10.6% vs 11.4%, with serious infections occurring in 0% vs 1.9%. No deaths occurred during the study.

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Highlights in Ulcerative Colitis From the 17th Congress of the European Crohn's and Colitis Organisation: Commentary

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The 17th Congress of the European Crohn's and Colitis Organisation (ECCO) had been scheduled to take place in Vienna, Austria, but was reorganized as a virtual conference based on ongoing concerns about the COVID-19 pandemic. Many advances in the field were shared at the meeting. Here I discuss some of the clinically relevant abstracts about ulcerative colitis, which provided data for treatments such as ozanimod, Janus kinase (JAK) inhibitors, and selective interleukin (IL) 23 inhibitors.

Ozanimod

Ozanimod is the newest available therapy for ulcerative colitis. Ozanimod is a first-in-class sphingosine 1-phosphate (S1P) receptor modulator that is approved by the US Food and Drug Administration for the treatment of moderately to severely active ulcerative colitis in adults.[1] This mechanism is unique in the field of inflammatory bowel disease. Ozanimod is an oral small molecule that targets the signaling molecule S1P, and thereby blocks activated lymphocytes from trafficking through the lymphatic system to reach the inflamed bowel. S1P receptor modulators are also used to treat multiple sclerosis, and ozanimod is approved in this setting. At the 17th Congress of ECCO, several presentations provided efficacy and safety analyses of the pivotal phase 3 True North study of ozanimod.[2]

Dr Britta Siegmund, the president of ECCO, and colleagues presented data summarizing the rapidity of onset of ozanimod therapy in the True North study.[2,3] Ozanimod has a cellular mechanism of control. It was thought that drugs with cellular mechanisms might have slower activity and onset than those based on cytokine inhibition. It appears, however, that cellular turnover in active ulcerative colitis is rapid,[4] and therefore blocking the cellular trafficking can result in speedy responses. This subset analysis measured the rapidity of onset in patients who received ozanimod compared with placebo. Statistically significant benefits for ozanimod vs placebo for symptomatic response and symptomatic remission were apparent as early as 2 and 5 weeks, respectively, after treatment began. Importantly, among patients previously treated with a tumor necrosis factor (TNF) inhibitor, ozanimod improved symptomatic response 4 weeks after treatment began. Among patients who were TNF-naive, ozanimod improved symptomatic response 2 weeks after initiation of treatment. For symptomatic remission, improvements were noted at 8 weeks for TKI-exposed patients and at 4 weeks for TNF-naive patients. Rapidity of onset is an important feature of ozanimod. It can signal to clinicians that the therapy is starting to exert an effect, while quickly improving symptoms for patients.

Dr Bruce Sands and colleagues presented a post hoc analysis of the True North study that evaluated the efficacy of ozanimod according to prior treatment exposure.[5] The analysis focused on patients treated unsuccessfully with 5-aminosalicylic acid therapies and who had not received prior immunomodulators or biologic therapies. In these patients, ozanimod was superior to placebo. Ozanimod was an effective treatment for corticosteroid-free induction. This analysis suggests that ozanimod can and should be used earlier in the treatment course, rather than saved for the most refractory patients.

Dr Silvio Danese and colleagues analyzed the long-term use of ozanimod in patients with ulcerative colitis, based on data from an open-label extension of the True North study.[6] Among the 823 patients who entered the open-label extension at the time of this analysis, the total patient-year exposure was 1201 years, and the mean duration of exposure to ozanimod was 1.5 years. Among patients who remained on therapy, efficacy assessments at 46 weeks, 94 weeks, and 142 weeks demonstrated stable rates of response and remission.

Notably, 116 patients had reached 142 weeks of treatment at the time of the presentation. An important finding was that the primary reason patients withdrew from the open-label extension was loss of response or lack of efficacy, which occurred in 21% of the patients. Only 5% of patients discontinued treatment due to adverse events. This reassuring finding suggests that when ozanimod is working, the

efficacy lasts, as has been seen with other therapies.

Dr Alessandro Armuzzi and colleagues presented an analysis of the safety of ozanimod, focusing on cardiovascular events.[7] This analysis combined data from the True North study with two phase 3 studies of ozanimod in patients with multiple sclerosis.[2,8,9] Reassuringly, ozanimod appears to be a very safe therapy. Other S1P targets can affect cardiac conduction. There has been interest in whether cardiac events might occur with ozanimod, even though this agent does not specifically target the S1P3 mechanism. The dose of the drug is titrated in the first week to mitigate any potential transient bradycardia. The follow-up analysis of these large phase 3 trials did not identify any issues with heart rate. There was only a slight increase in mean blood pressure, which stabilized over time. Treatment with ozanimod was not associated with any major adverse cardiovascular events in either of these disease states.

JAK Inhibitors

Several selective JAK-1 inhibitors are in development for ulcerative colitis. Dr Séverine Vermeire and colleagues presented a study of the efficacy and safety of an extended induction treatment strategy with upadacitinib at 45 mg/day, followed by maintenance with upadacitinib at 15 mg/day or 30 mg/day.[10] This study explored questions that have arisen in the community regarding the delayed response and remission that can occur with some of the therapies. For example, will extending induction therapy beyond the standard duration increase response rates? Does a delayed response or remission impact a patient's long-term outcome?

These questions were addressed by the recommended dosing for tofacitinib, which can be administered for up to 16 weeks as induction therapy.[11] For upadacitinib, the study by Dr Vermeire showed that an additional 8 weeks of treatment at 45 mg/day led to a clinical response in 48% of patients, with an additional 6% of patients achieving clinical remission. Importantly, the patients who achieved these results after the extended induction period of 16 weeks also received maintenance therapy. This analysis showed that the 30-mg maintenance dose was superior to the 15-mg dose. These data suggest that treatment with upadacitinib should not be stopped too soon. Of course, treatment should not continue if the patient is not doing well or getting worse. These data provide reassurance that patients who take longer to achieve remission will have the same outcomes as those who respond more quickly. These data also serve as a reminder that the 30-mg maintenance dose appears to be more effective in this group of patients.

Dr Silvio Danese and colleagues described the effects of maintenance therapy with upadacitinib on the secondary endpoints of abdominal pain, bowel urgency, and fatigue among patients enrolled in the phase 3 U-ACHIEVE maintenance study.[12] The analysis demonstrated that the dose of 45 mg for induction therapy reduced rates of patient-reported abdominal pain, urgency, and fatigue. Among patients who responded to induction therapy, these important endpoints continued to improve through week 52 of maintenance treatment. At the end of this analysis, the 30-mg dose of upadacitinib again demonstrated numerically higher efficacy and improvement of these endpoints than the 15-mg dose as compared with placebo. The inclusion of fatigue and urgency in ongoing studies of ulcerative colitis reflects the importance of these symptoms.

Dr Stefan Schreiber and colleagues explored novel co–primary endpoints in the SELECTION study of filgotinib.[13] This post hoc analysis combined the endpoints of clinical, biological, and health-related quality-of-life remission, plus endoscopic improvement. The analysis showed that quality of life overall was improved among the patients who met this combined endpoint. This study suggests that evaluation of single endpoints

ABSTRACT SUMMARY Exploring Disease Control by Combining Clinical, Biological, and Health-Related Quality of Life Remission With Endoscopic Improvements Among Ulcerative Colitis Patients Treated With Filgotinib: A Post-Hoc Analysis From the SELECTION Trial

The phase 2b/3 SELECTION trial evaluated the safety and efficacy of filgotinib for treating patients with moderately to severely active ulcerative colitis (Abstract OP07). Patients were divided into 2 cohorts based on prior exposure to biologic therapy. Patients in each cohort were randomly assigned 2:2:1 to receive daily filgotinib at 200 mg, filgotinib at 100 mg, or placebo for 11 weeks of induction treatment, followed by 47 weeks of maintenance therapy in patients with a clinical remission or response after induction. A post hoc analysis of the SELECTION trial evaluated a combined endpoint that included clinical remission, endoscopic improvement, biological remission, and remission based on the inflammatory bowel disease questionnaire. Among biologic-naive patients, those treated with filgotinib at 200 mg were more likely to achieve the combined endpoint compared with patients who received placebo, both at week 10 (17.6% vs 4.41%; $P<.001$) and week 58 (22.1% vs 7.14%; $P=.002$). Patients who achieved the combined endpoint also experienced clinically meaningful improvements in their overall quality of life.

separated from other measures of interest may not be the most effective way to measure the overall treatment effect. Further exploration of combined endpoints such as this one—including complex, health-related quality-of-life measures—is ongoing.

Selective IL-23 Inhibitors

Selective IL-23 inhibitors target the p19 subunit of IL-23. In contrast, the currently approved IL-12/23 inhibitor, ustekinumab, targets p40.[14] Dr Geert D'Haens presented data for the efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active ulcerative colitis in the phase 3 LUCENT-1 study.[15] At week 12, mirikizumab at an intravenous dose of 300 mg was superior to placebo, with a response rate of 63.5%. Improvements were seen in both biologic-naive and biologic-exposed patients. As with many other therapies, rates of response and remission were higher in patients who were biologic-naive. In these patients, the response rate was 70.1%.

At week 12, the remission rate with mirikizumab was 24.2%, an 11% improvement vs placebo. In biologic-naive patients, the remission rate was 30.9%. A notable observation regarding symptoms is that mirikizumab improved bowel urgency in as quickly as 2 weeks, and the improvement persisted during 12 weeks of induction therapy. Therefore, patients who respond to mirikizumab will do so rapidly.

Guselkumab is another p19 agent in development for ulcerative colitis. Dr Axel Dignass presented results of the phase 2b QUASAR study, which evaluated guselkumab as induction therapy for moderate to severe ulcerative colitis.[16] This 12-week study compared 2 doses of guselkumab, 200 mg or 400 mg administered intravenously every 4 weeks, vs placebo given intravenously at the same schedule. At both doses, guselkumab was superior to placebo. The response rate for each dose was approximately 61%, and the rate of clinical remission was approximately 25%. The remission rate with placebo was only 9.5%. The safety of guselkumab was excellent, similar to that of the other IL-23 inhibitors. There were no additional safety signals of interest.

Dr Bruce Sands and colleagues provided data from one of my favorite studies presented at ECCO, which evaluated combination induction therapy with guselkumab and the anti-TNF therapy golimumab in patients with moderate to severe ulcerative colitis.[17] The study was a phase 2a, randomized, double-blind, active-control, parallel-group, proof-of-concept trial that evaluated each agent as monotherapy, as well as combined. Data were provided for the 12-week endpoint. The principle behind the study was based on preclinical data in mice suggesting that IL-23 and TNF may play a role in active colitis.[18] Therefore, there is a rationale to combine different anticytokine therapies.

The combination regimen was numerically superior to monotherapy with either treatment. The difference reached statistical significance for the comparison of the combination vs golimumab. The rate of clinical response was 83.1% with the combination therapy (P=.003 vs golimumab), 74.6% with guselkumab, and 61.1% with golimumab. The remission rate was 36.6% with the combination therapy, 21.1% with guselkumab, and 22.1% with golimumab. Endoscopic improvement and endoscopic normalization (defined as an endoscopic subscore of 0) were also better with the combination vs each monotherapy.

This phase 2 proof-of-concept study supports the strategy of combining drugs with different mechanisms of action. The safety of the combination appeared to be acceptable. Further work in combining novel mechanisms is warranted to try to break the current therapeutic ceiling in ulcerative colitis.

ABSTRACT SUMMARY Development of a Novel Ulcerative Colitis Endoscopic Activity Prediction Model Using Machine Learning

Jean-Frederic Colombel, MD, and colleagues developed a novel ulcerative colitis endoscopic activity prediction model that used machine learning trained on endoscopic Mayo score features using centrally read endoscopies (Abstract DOP59). The prediction model was based on 793 full-length videos obtained from 249 patients with ulcerative colitis who participated in a phase 2 trial of mirikizumab. The machine-learning workflow consisted of annotation, segmentation, and classification (eg, erosions, ulcers, erythema, vascular pattern, and bleeding). On the full test set of 147 videos, the model predicted for inactive disease vs active disease with an accuracy of 84%, a positive predictive value of 80%, and a negative predictive value of 85%. In the subset of 94 videos with centrally read endoscopic Mayo scores and annotator-reported endoscopic Mayo scores, the model predicted inactive disease compared with active disease with an accuracy of 89%, a positive predictive value of 87%, and a negative predictive value of 90%. The authors concluded that this machine-learning predictive model was able to distinguish between active and inactive disease, and could identify other levels of endoscopic endpoints, such as healing and severe disease.

Dr Jean-Frederic Colombel and I were among the coinvestigators of a study that examined a novel ulcerative colitis endoscopic activity prediction model using machine learning.[19] The machine-learning predictive model of the endoscopic Mayo score used recorded videos taken from patients enrolled in phase 3 studies of mirikizumab. The complexity of developing machine-learning models is of interest. More importantly, this strategy of using artificial intelligence to read endoscopic activity demonstrated excellent distinction between active and inactive disease, and clear discrimination between other levels of endoscopic activity. The use of such a model may eliminate the need for clinicians to evaluate outcomes in trials, which is time-consuming and expensive. This type of model could also revolutionize the way clinicians in practice interpret endoscopic activity during routine scopes of patients with ulcerative colitis.

Conclusion

The field of ulcerative colitis continues to rapidly advance. This summary of clinically relevant abstracts from ECCO provides an update on some of the most exciting developments. There are certainly more to come.

Disclosure

Dr Rubin has received grant support from Takeda, and he has served as a consultant for AbbVie, AltruBio, Arena Pharmaceuticals, Bristol Myers Squibb, Genentech/Roche, Gilead Sciences, Iterative Scopes, Janssen Pharmaceuticals, Lilly, Pfizer, Prometheus Biosciences, Takeda, and TechLab Inc.

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