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A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis From the American College of Gastroenterology 2024 Annual Scientific Meeting

A Review of Selected Presentations From the ACG 2024 Annual Scientific Meeting
October 25-30, 2024 • Philadelphia, Pennsylvania

Special Reporting on:

- Efficacy and Safety of Guselkumab Maintenance Therapy Among Guselkumab Induction Week 24 Clinical Responders: Results From the Phase 3 QUASAR Maintenance Study
- Efficacy, Safety and Immunogenicity of Subcutaneous Infliximab (CT-P13 SC) Monotherapy vs Combination Therapy With Immunosuppressants – Post Hoc Analysis of LIBERTY-CD and LIBERTY-UC Studies
- The Efficacy of Maintenance Treatment With Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 3 QUASAR Maintenance Study Results at Week 44 by Biologic/Janus Kinase Inhibitor History
- Long-Term Endoscopic and Histological Outcomes of Mirikizumab in Patients With Moderately to Severely Active Ulcerative Colitis With Up to 3 Years of Treatment
- Efficacy of Risankizumab Maintenance Therapy by Clinical Remission and Endoscopic Improvement Status in Patients With Moderately to Severely Active Ulcerative Colitis: Post Hoc Analysis of the COMMAND Phase 3 Study
- Corticosteroid-Sparing Effects of Treatment With Guselkumab in Patients With Moderate to Severely Active Ulcerative Colitis: Phase 3 QUASAR Maintenance Study Results Through Week 44
- Corticosteroid-Free Remission Through 3 Years of Upadacitinib Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Data From the Phase 3 Long-Term Extension Study U-ACTIVATE
- Histologic and Combined Histologic and Endoscopic Outcomes After Guselkumab Maintenance Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Week 44 Results From the Phase 3 QUASAR Maintenance Study
- Safety of Long-Term Ozanimod Treatment Up to 5 Years in Patients With Moderately to Severely Active Ulcerative Colitis: An Interim Analysis of the True North Open-Label Extension

PLUS Meeting Abstract Summaries

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Efficacy and Safety of Guselkumab Maintenance Therapy Among Guselkumab Induction Week 24 Clinical Responders: Results From the Phase 3 QUASAR Maintenance Study

Guselkumab is a fully human selective interleukin-23 (IL-23) inhibitor that blocks IL-23 and binds to CD64, a receptor expressed on IL-23-producing cells. In September 2024, guselkumab received US Food and Drug Administration (FDA) approval for the treatment of adults with moderately to severely active ulcerative colitis (UC).[1] This approval was based on results from the phase 2b/3 QUASAR trial, which evaluated guselkumab in adults with moderately to severely active UC who had an inadequate response or intolerance to conventional therapy, other biologics, and/or Janus kinase (JAK) inhibitors.[2,3]

The randomized, double-blind, placebo-controlled, parallel-group, multicenter QUASAR trial protocol included a phase 2b dose-ranging induction study, a phase 3 induction study, and a phase 3 randomized withdrawal maintenance study. The maintenance study evaluated the efficacy and safety of 2 dose schedules of subcutaneous (SC) guselkumab maintenance (200 mg every 4 weeks or 100 mg every 8 weeks) vs placebo (guselkumab withdrawal) in patients who had attained a clinical response to 12 weeks of intravenous (IV) guselkumab in the induction trials.

Patients without a response to IV guselkumab at induction week 12 (I-12) received SC guselkumab maintenance every 4 weeks; 60.6% attained a clinical response by week I-24 and then entered the maintenance study phase and continued SC guselkumab 200 mg every 4 weeks. Rubin and colleagues evaluated the patients in this subgroup of guselkumab week I-24 responders separately from the randomized population. Efficacy outcomes were reported for maintenance week 44, and safety was assessed throughout the maintenance period.[4] The analysis included 123 patients with a modified Mayo score (MMS) of 5 to 9 at induction baseline who received at least 1 dose of guselkumab maintenance. Overall, the population of guselkumab week 1-24 responders had a high UC severity at baseline of induction therapy: 74.8% had severe disease defined as an MMS of 7 to 9, 77.2% had a Mayo endoscopic subscore of 3, and 48% had extensive UC. The median C-reactive protein was 5.0 mg/L. More than half of patients (59.3%) had a history of inadequate response or intolerance to biologic and/or JAK inhibitor therapy, and 46.6% had received at least 2 biologics and/or JAK inhibitors.

At maintenance week 44, 67.5% of the week 1-24 responders demonstrated a maintenance of

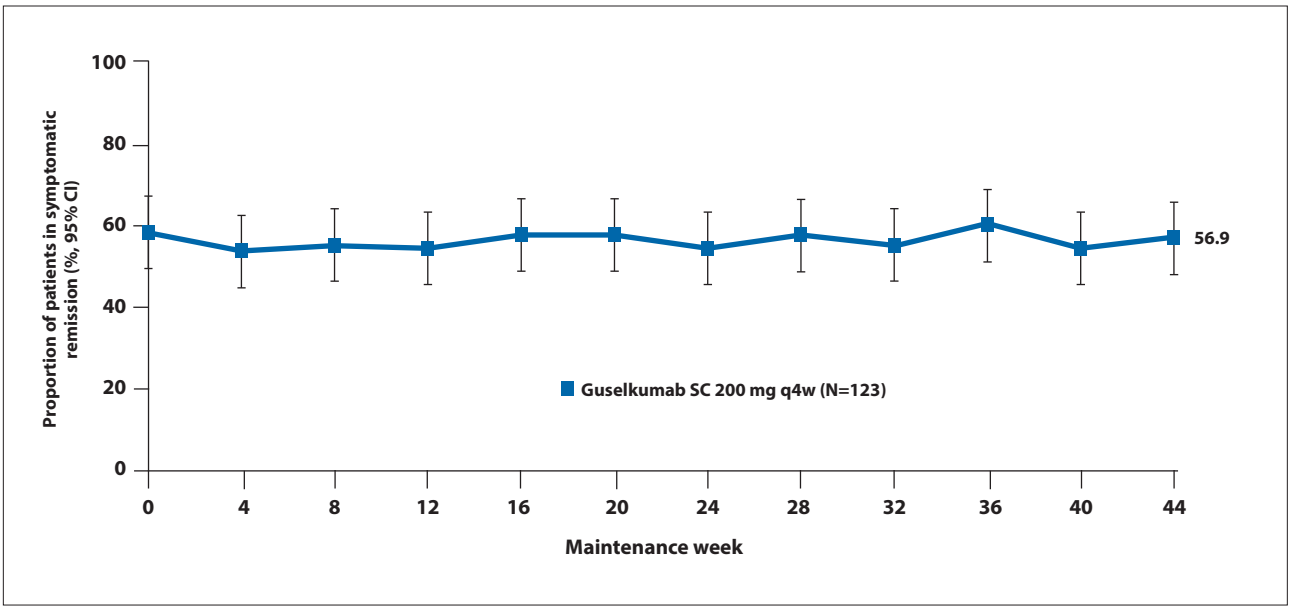

Figure 1. Symptomatic remission over time in the phase 3 QUASAR maintenance study in patients with moderately to severely active ulcerative colitis who were clinical responders to guselkumab at induction week 24.

q4w, every 4 weeks; SC, subcutaneous.

Adapted from Rubin DT, et al. Abstract P0826. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[4]

Of the patients who did not initially respond to 3 induction doses, 60.6% (123 of 203) achieved clinical response to 3 further doses and entered the maintenance study phase. This more refractory population of UC patients (who did not respond initially by week 12 but did respond after 3 further doses of guselkumab 200 mg SC at weeks 12, 16, and 20) had higher UC disease burden and were able to maintain or improve endoscopic, histologic, symptomatic, and QOL outcomes. Safety results were consistent with the overall population and safety profile of guselkumab in its approved indications. Overall, the results support continuing guselkumab treatment in this more refractory patient population.

—Gary R. Lichtenstein, MD

clinical response, 30.1% achieved clinical remission (CR), 30.1% had corticosteroid-free CR, and 56.9% had symptomatic remission (Figure 1). Symptomatic remission was defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline and a rectal bleeding subscore of 0. Of the 20 patients in CR at maintenance baseline, 50% maintained CR at maintenance week 44.

Endoscopic improvement and histo-endoscopic mucosal improvement were achieved in 35.8% and 27.6% of patients, respectively, and 17.1% achieved endoscopic remission (normalization). Quality of life (QOL) outcomes were assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ) and a Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue instrument. At maintenance week 44, 54.5% of the guselkumab week 1-24 responders achieved IBDQ remission and 39.8% achieved a fatigue response on the PROMIS Fatigue Short Form 7.

In the safety analysis, the overall rate of adverse events (AEs) among guselkumab week 1-24 responders was 78.0%, including 5.7% serious AEs and 4.1% AEs leading to discontinuation. Infections occurred in 43.1% of patients, and serious infections occurred in 1.6%. No cases of active tuberculosis, anaphylaxis, serum sickness, opportunistic infections, major adverse cardiovascular events, or clinically important hepatic disorders were reported. There was 1 report of a malignancy consisting of an unrelated renal cell carcinoma.

The study authors concluded that, in this refractory population of patients with a higher UC disease burden at baseline, continued treatment with SC guselkumab 200 mg every 4 weeks resulted in the maintenance or improvement of endoscopic, histologic, symptomatic, and QOL outcomes. No new safety findings were noted.

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4. Rubin DT, Dignass A, Allegretti JR, et al. Efficacy and safety of guselkumab maintenance therapy among guselkumab induction week 24 clinical responders: results from the phase 3 QUASAR maintenance study. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P0826.

Efficacy, Safety and Immunogenicity of Subcutaneous Infliximab (CT-P13 SC) Monotherapy vs Combination Therapy With Immunosuppressants – Post Hoc Analysis of LIBERTY-CD and LIBERTY-UC Studies

In the randomized, double-blind LIBERTY trials, SC administration of the infliximab biosimilar CT-P13 (CT-P13 SC) demonstrated superior efficacy over placebo as maintenance therapy for up to 1 year in patients with moderate to severe Crohn's disease (CD) or UC.[1] An extension phase demonstrated continued efficacy and tolerability of CT-P13 SC as maintenance treatment for up to 2 years in patients with moderate to severe CD and UC.[2,3]

In a post hoc analysis, Sands and colleagues evaluated outcomes with CT-P13 SC maintenance based on patients' baseline immunosuppressant use.[4] The trial had permitted immunosuppressant use (azathioprine, 6-mercaptopurine, or methotrexate) in patients who maintained stable doses

for at least 8 weeks prior to week 0. The post hoc analysis included patients who had received CT-P13 SC 120 mg every 2 weeks as maintenance therapy, comparing outcomes based on whether patients received CT-P13 SC without immunosuppressants (monotherapy; 180 patients with UC) or with immunosuppressants (combination therapy; 57 patients with UC). Among the 57 patients with UC who received combination therapy, immunosuppressants used included azathioprine (96.5%) and 6-mercaptopurine (3.5%).

Overall, no meaningful differences in efficacy outcomes were observed at weeks 54 or 102 regardless of whether patients had received CT-P13 SC maintenance as monotherapy or in combination with immunosuppressants. In a nonresponder imputation analysis, which considered patients with CT-P13 SC dose adjustments to 240 mg as nonresponders, week 54 CR rates with monotherapy and combination therapy were 52% and 56%, respectively, and week 102 CR rates were 47% and 39%, respectively. Endoscopic-histologic mucosal improvement rates with monotherapy and combination therapy were 43% and 47%, respectively, at week 52, and 44% and 33%, respectively, at week 102.

In an analysis that did not consider patients with dose adjustments as nonresponders, week 54 CR rates with monotherapy and combination therapy were 60% and 65%, respectively, and week 102 CR rates were 56% and 54%, respectively (Figure 2). Endoscopic-histologic mucosal improvement rates with monotherapy and combination therapy were 51% and 53%, respectively, at week 54, and 50% and 51%, respectively, at week 102.

Pharmacokinetics results showed that among patients with UC, the proportion of patients in the lowest tertile of pre-dose concentration trough at week 54 was lower with combination therapy compared with monotherapy. This difference was no longer observed at week 102. Remission rates were generally lower in patients with the lowest tertile drug concentration, and no

> Post hoc analysis of data from this prospective study found no significant difference in efficacy of therapy in patients who had a clinical response or patients on monotherapy or on immunosuppression at week 52 or 104. Although the rate of antidrug antibodies was lower with combination therapy, there was no difference in efficacy, biomarker profiles, or safety outcomes. If this study was conducted in a fashion similar to the SONIC trial, in which half of patients were prospectively randomized to monotherapy and half were given combination therapy, differences may have been observed, such as better outcomes in those on an immunomodulator and CT-P13 SC.
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> —Gary R. Lichtenstein, MD

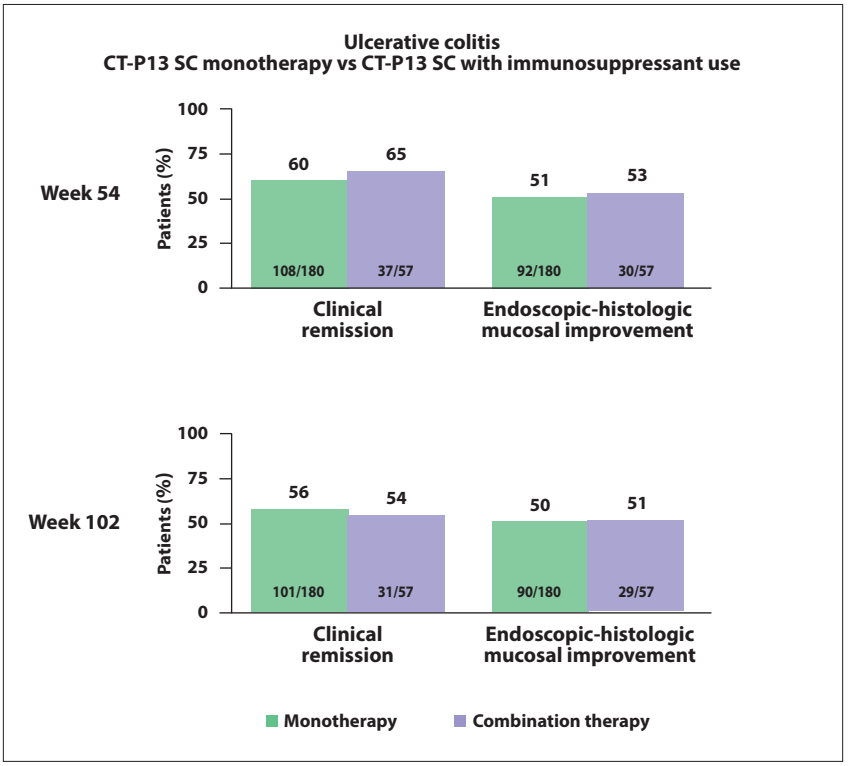

Figure 2. The efficacy of subcutaneous infliximab (CT-P13 SC) monotherapy vs combination therapy in the LIBERTY-UC study in patients with moderate to severe ulcerative colitis at weeks 54 and 102.

Adapted from Sands BE, et al. Abstract 44. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[4]

consistent differences between monotherapy and combination therapy were reported within drug concentration tertiles. Biomarker studies and safety analyses were comparable between monotherapy and combination therapy. Combination therapy led to lower formation of antidrug antibodies with higher drug levels that did not lead to differences in efficacy outcomes.

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The Efficacy of Maintenance Treatment With Guselkumab in Patients With Moderately to Severely Active Ulcerative Colitis: Phase 3 QUASAR Maintenance Study Results at Week 44 by Biologic/Janus Kinase Inhibitor History

The phase 3 QUASAR maintenance study examined the efficacy and safety of guselkumab maintenance treatment compared with placebo, based on history of treatment with biologics and/or JAK inhibitors.[1]

The study enrolled adults with moderately to severely active UC, defined as induction baseline MMS of 5 to 9 (with a Mayo rectal bleeding subscore ≥1 and a Mayo endoscopic subscore ≥2) during central review of the screening endoscopy, with an inadequate response or intolerance to conventional therapy and/or biologic and/or JAK inhibitor therapy. Patients were randomly assigned to guselkumab 200 mg SC every 4 weeks, guselkumab 100 mg SC every 8 weeks, or placebo (guselkumab withdrawal) for a 44-week period followed by a long-term extension (LTE).

Overall, 56% (309) of patients were biologic/JAK-naive and 44% (240) had received biologics or JAK inhibitors. The biologic/JAK-treated patients accounted for 42% of those in the guselkumab 100 mg arm, 48% in the guselkumab 200 mg arm, and 41% in the placebo arm.

According to Allegretti and colleagues, maintenance treatment with guselkumab was associated with improvements in clinical, endoscopic, and histologic endpoints at week 44.[1] In the overall population, week 44 CR rates were 45.2% and 50.0% with guselkumab 100 mg and 200 mg, respectively, compared with 18.9% with placebo (Figure 3). Week 44 symptomatic remission rates were 70.2%, 68.9%, and 37.4%, respectively. Week 44 histo-endoscopic mucosal improvement rates were 43.6%, 47.9%, and 16.8%, respectively, and week 44 endoscopic remission rates were 34.6%, 33.7%, and 15.3%, respectively. Each of the

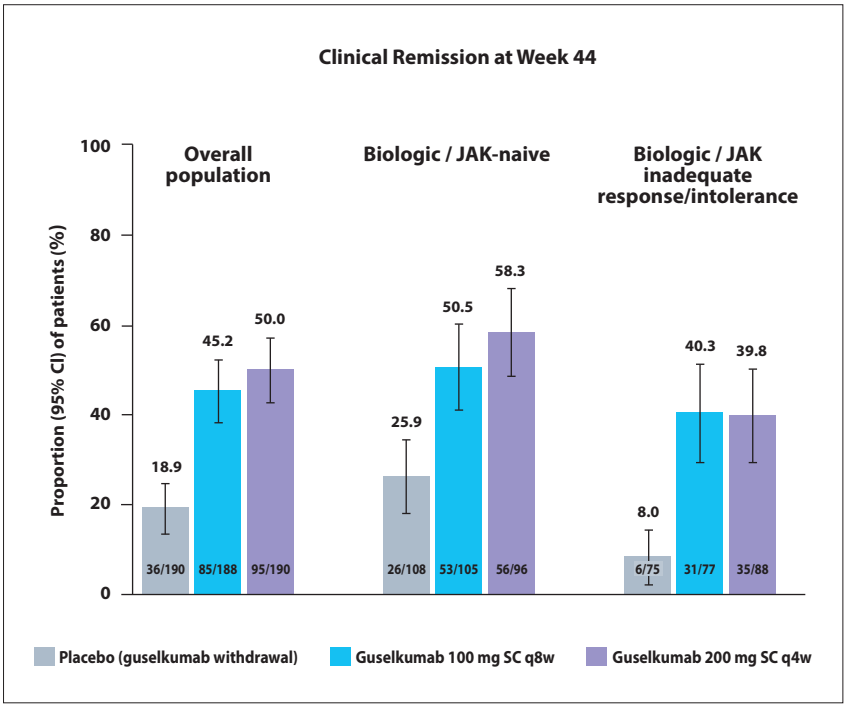

Figure 3. Clinical remission at week 44 with guselkumab maintenance treatment compared with placebo in the phase 3 QUASAR maintenance study in patients with moderately to severely active ulcerative colitis who had inadequate response/intolerance to conventional therapy and/or biologic and/or JAK inhibitor therapy.

JAK, Janus kinase inhibitor; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous.

Adapted from Allegretti J, et al. Abstract P2580. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[1]

outcomes was improved with guselkumab vs placebo (guselkumab withdrawal) regardless of whether patients had received a prior biologic and/or JAK inhibitors.

Safety outcomes were consistent with the known safety profile of guselkumab.[2] The rates of serious AEs with guselkumab and placebo were 4.5% and 0.5%, respectively, in the overall population; 4.0% and 0.9%, respectively, in biologic/JAK-naive patients; and 4.9% and 0%, respectively, in biologic/JAK-treated patients. Other safety outcomes were also consistent regardless of whether patients had received a prior biologic and/or JAK inhibitors.

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1. Allegretti J, Panés L, Peyrin-Biroulet BE, et al. The efficacy of maintenance treatment with guselkumab in patients with moderately to severely active ulcerative colitis: phase 3 QUASAR maintenance study results at week 44 by biologic/Janus kinase inhibitor history. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P2580.
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It is recognized that individuals with prior exposure to anti–tumor necrosis factor (TNF) drugs often have a lower chance of success with subsequent anti-TNF therapies (ie, the effectiveness may be reduced and patients may be less likely to achieve remission or may require switching to a different medication class altogether). Similar findings have been seen with S1P receptor modulators. This study evaluated pooled induction data from 4 randomized controlled trials (1562 patients) and related that S1P receptor modulators may be more effective in inducing CR compared with placebo in patients with moderately to severely active UC and prior biologic exposure. The same finding has been seen in UC patients with prior biologic use who initiate JAK inhibitor therapy, whereas the GEMINI trials have shown that vedolizumab is more effective in patients who have not previously received anti-TNF medications compared with patients with prior failure of anti-TNF therapy.

—Gary R. Lichtenstein, MD

Long-Term Endoscopic and Histological Outcomes of Mirikizumab in Patients With Moderately to Severely Active Ulcerative Colitis With Up to 3 Years of Treatment

Mirikizumab is a p19-directed anti-IL-23 antibody that received FDA approval in 2023 for use in adults with moderately to severely active UC. Its approval was based on the results of the LUCENT-1 and LUCENT-2 trials, which demonstrated greater efficacy with mirikizumab over placebo for inducing and maintaining CR in patients with moderately to severely active UC.[1,2]

The blinded LUCENT-1 trial enrolled patients who had an MMS of 4 to 9, an endoscopic subscore of 2 or 3, and an inadequate response, loss of response, or intolerance to 1 or more corticosteroid, immunomodulator, or up to 3 biologic therapies or a JAK inhibitor for UC. Patients were randomly assigned 3:1 to mirikizumab 300 mg IV every 4 weeks (n=868) or placebo (n=294). Patients who attained a response at week 12 (n=544) were enrolled in the blinded LUCENT-2 trial, in which they were randomly assigned 2:1 to maintenance mirikizumab 200 mg SC every 4 weeks (n=365) or placebo (n=179). A total of 266 patients completed the week 52 visit (week 40 of LUCENT-2) and were enrolled in the LUCENT-3 LTE study, in which they received mirikizumab for an additional 100 weeks, for a total treatment period of 152 weeks.

Sands and colleagues evaluated the long-term endoscopic and histologic outcomes through 3 years among patients with moderately to severely active UC who attained CR at week 52 after blinded mirikizumab maintenance in the LUCENT-2 trial and continued to the single-arm, open-label, phase 3 LUCENT-3 LTE study.[3]

In the LUCENT-3 trial, 154 patients had achieved CR at week 52 after mirikizumab maintenance. The mean age of clinical remitters was 43.2 years; 59.1% were male and 73.0% were White. The mean disease duration was 5.6 years, mean MMS was 6.7, and 68.8% had a severe endoscopic subscore. Nearly one-third of patients (30.5%) had prior biologic or tofacitinib failure.

In an observed case analysis, 81%

This study demonstrated that mirikizumab maintained endoscopic and histologic outcomes through an additional 2 years of continuous treatment for a total of 3 years. In addition, individuals who achieved long-term durable and sustained endoscopic and histologic outcomes with mirikizumab had in aggregate achieved an overall better health-related QOL. Remarkably, nearly three-quarters (70%) of patients who achieved CR at week 52 were able to achieve histologic and endoscopic remission without neutrophils on histology at week 152, and nearly half (47%) of all clinical remitters at week 52 were able to achieve endoscopic normalization at week 152.

—Gary R. Lichtenstein, MD

of patients had CR at week 152, 82% had endoscopic remission, 75% had histologic improvement, 71% had histologic remission, 71% had histologic-endoscopic mucosal improvement, 70% had histologic-endoscopic remission, 47% had endoscopic normalization, and 44% had alternate histologic-endoscopic remission (Figure 4). A modified nonresponder imputation analysis yielded similar findings.

There was a strong association between attaining clinical and endoscopic endpoints with mirikizumab at week 152 and improved health-related QOL; 93% of patients who achieved CR, endoscopic remission, histologic remission, or histologic-endoscopic remission at week 152 also had IBDQ remission.

The study authors concluded that 3 years of mirikizumab was associated with maintenance of endoscopic and histologic outcomes, and these long-term sustained outcomes were associated with better health-related QOL.

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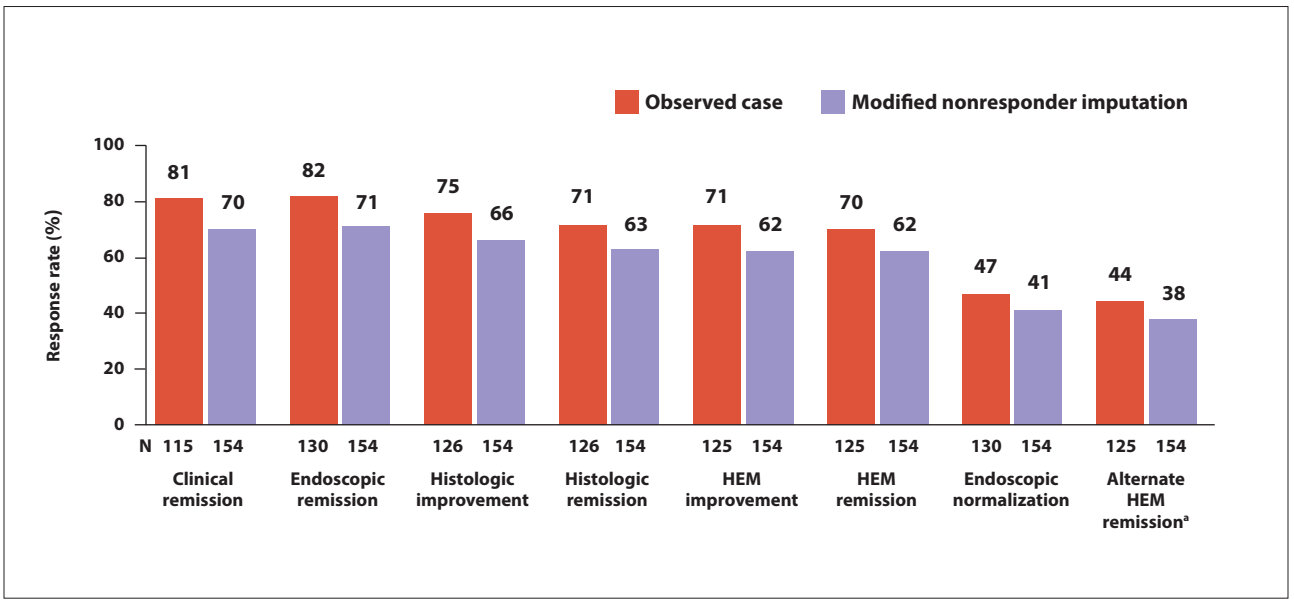

Figure 4. Proportion of patients with moderately to severely active ulcerative colitis on mirikizumab achieving clinical endpoints at week 152 in the LUCENT-3 long-term extension study. HEM, histologic-endoscopic mucosal; N, number of participants in the analysis population. [a]Histologic remission + endoscopic normalization.

Adapted from Sands B, et al. Abstract P4354. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[3]

Efficacy of Risankizumab Maintenance Therapy by Clinical Remission and Endoscopic Improvement Status in Patients With Moderately to Severely Active Ulcerative Colitis: Post Hoc Analysis of the COMMAND Phase 3 Study

Risankizumab is a p19-targeting anti-IL-23 monoclonal antibody that received FDA approval in 2024 for use in adults with moderately to severely active UC. The approval was based on results from the 12-week INSPIRE induction study and the 52-week COMMAND maintenance study, in which risankizumab demonstrated superior CR rates over placebo.[1,2]

In the INSPIRE induction study, patients with moderately to severely active UC were randomly assigned 2:1 to receive IV risankizumab 1200 mg or placebo; patients with a clinical response to IV risankizumab induction were enrolled in the COMMAND study and randomly assigned 1:1:1 to receive SC risankizumab 180 mg, SC risankizumab 360 mg, or placebo (risankizumab withdrawal).

In a post hoc analysis, Panaccione and colleagues evaluated outcomes in the COMMAND phase 3 study based on CR and endoscopic improvement (EI) status upon entering the maintenance study.[3] Demographic and disease characteristics were generally balanced at baseline of the induction period. At baseline of the maintenance period, the mean disease duration was longer in patients who had not achieved CR or EI (7.1-7.9 years) than in those who had (5.0-6.8 years).

The population of overall responders included all randomized patients who received at least 1 dose of maintenance treatment after receiving IV risankizumab 600 mg, 1200 mg, or 1800 mg in the induction study.

At week 52 in the COMMAND maintenance study, clinical, endoscopic, and histologic outcomes were generally better with risankizumab vs placebo, regardless of CR or EI status at week 0 of maintenance therapy. Week 52 CR rates with risankizumab 180 mg, risankizumab 360 mg, and placebo were 70.2%, 50.0%, and 39.6%, respectively, in patients with CR at week 0, compared with 29.9%, 34.5%, and 19.5%, respectively, in patients without CR at week 0 (Figure 5). Endoscopic remission rates were 53.5%, 27.5%, and 22.6%, respectively, in patients with CR at week 0, compared with 13.4%, 23.6%, and 11.7%, respectively, in patients without CR at week 0.

Similarly, week 52 CR rates with risankizumab 180 mg, risankizumab 360 mg, and placebo were 58.9%, 41.2%, and 41.0%, respectively, in patients with endoscopic improvement at week 0, compared with 30.2%,

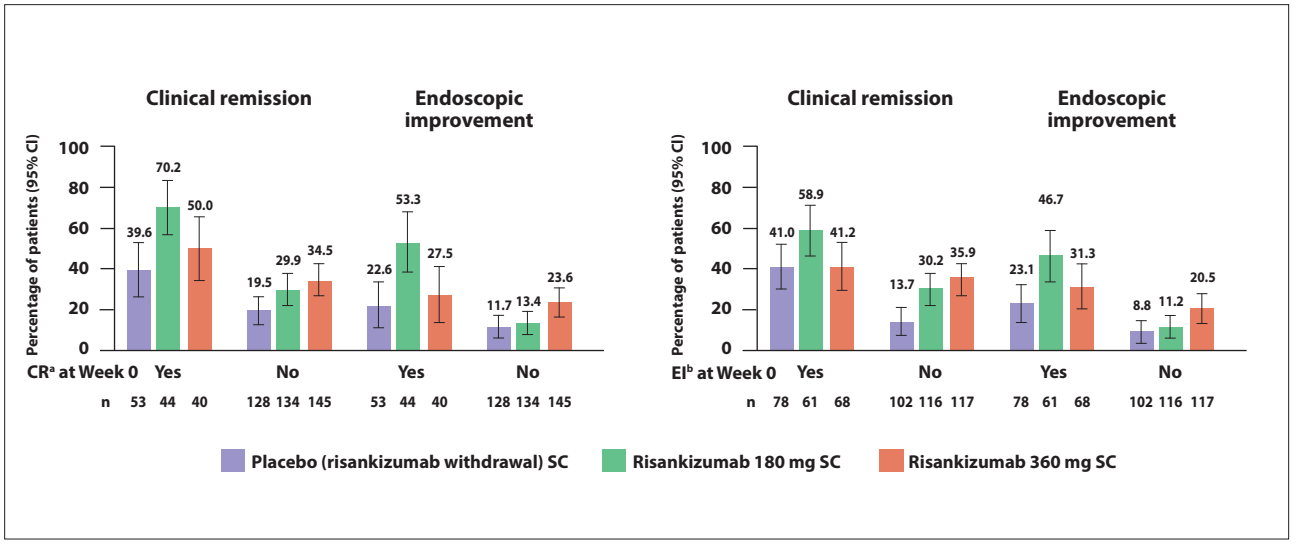

Figure 5. Clinical and endoscopic outcomes at week 52 in the COMMAND maintenance study according to clinical remission or endoscopic improvement status at week 0 of maintenance therapy with risankizumab for the overall responders population. SC, subcutaneous.

[a]Clinical remission: stool frequency score ≤1 and not greater than baseline, rectal bleeding score of 0, and endoscopic subscore ≤1.
[b]Endoscopic improvement: Mayo endoscopic subscore ≤1 without evidence of friability.

Adapted from Panaccione R, et al. Abstract P4377. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[3]

35.9%, and 13.7%, respectively, in patients without endoscopic improvement at week 0. Week 52 endoscopic remission rates were 46.7%, 31.3%, and 23.1%, respectively, in patients with endoscopic improvement at week 0, compared with 11.2%, 20.5%, and 8.8%, respectively, in patients without endoscopic improvement at week 0.

Among patients in the maintenance study who attained a clinical response to induction risankizumab but had not achieved CR or endoscopic improvement, SC risankizumab 360 mg was associated with greater rates of improvement over SC risankizumab 180 mg in all outcomes at maintenance week 52.

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A benefit with risankizumab compared with placebo was observed in patients with an inadequate response to prior nonadvanced therapy (29.7% vs 8.4%) and in patients with an inadequate response to prior advanced therapy (11.4% vs 4.3%). In this study, there were several important findings: (1) the proportion of patients who had prior failure to advanced therapy was numerically higher for patients who did not achieve CR or EI at maintenance week 0 than for those who achieved it; (2) the rates of each clinical, endoscopic, and histologic outcome were generally numerically higher with risankizumab vs placebo regardless of CR or EI status at maintenance week 52; and (3) among patients with clinical response to the induction treatment who did not achieve CR or EI, risankizumab 360 mg SC demonstrated numerically higher rates of improvement in all presented outcomes over risankizumab 180 mg SC at maintenance week 52. This study highlights that exposure to risankizumab was associated with improved outcome regardless of week 12 (early) outcomes.

—Gary R. Lichtenstein, MD

Corticosteroid-Sparing Effects of Treatment With Guselkumab in Patients With Moderate to Severely Active Ulcerative Colitis: Phase 3 QUASAR Maintenance Study Results Through Week 44

Minimizing corticosteroid use is an important goal of UC treatment.[1] An analysis of the QUASAR maintenance study by Bressler and colleagues examined the corticosteroid-sparing effects of treatment with guselkumab in patients with moderately to severely active UC. At baseline, up to 20 mg/day of prednisone or equivalent was permitted. A stable dose of oral corticosteroid was maintained in the induction study, and in the maintenance study, a mandatory corticosteroid taper was started at week 0.

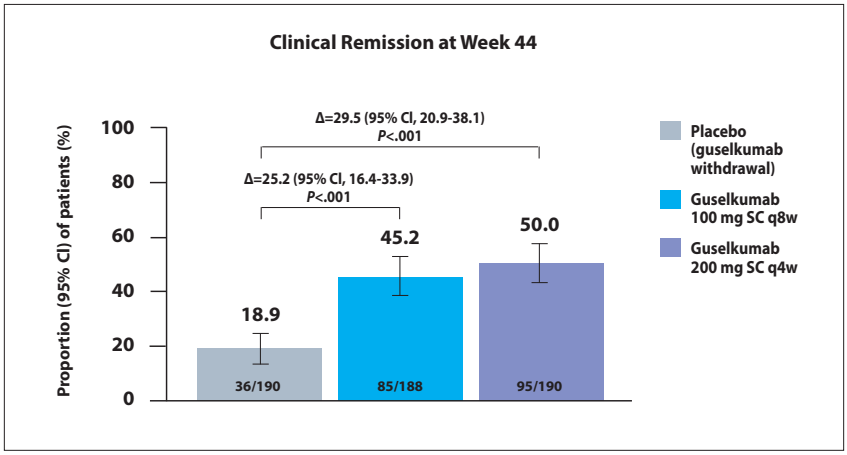

Figure 6. Clinical remission at week 44 in patients with moderately to severely active ulcerative colitis receiving guselkumab maintenance vs placebo who were able to eliminate corticosteroid use. q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous. Adapted from Bressler B, et al. Abstract P4307. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[1]

In the QUASAR phase 3 induction trial, guselkumab was demonstrated to be effective for achieving CR in patients with moderately to severely active UC. In the QUASAR randomized withdrawal maintenance study, 50.0% (*P*<.001) of patients with moderately to severely active UC receiving SC guselkumab 200 mg every 4 weeks and 45.2% (*P*<.001) of patients receiving SC guselkumab 100 mg every 8 weeks achieved the primary endpoint of CR at week 44 compared with placebo (18.9%). Among patients with moderately to severely active UC who were receiving concomitant oral corticosteroids at maintenance baseline, the majority of guselkumab-treated patients eliminated corticosteroids within 8 weeks. These impressive and clinically relevant findings highlight the fact that patients who were receiving maintenance treatment with guselkumab who achieved CR at week 44 did so without concomitant use of oral corticosteroids.

—Gary R. Lichtenstein, MD

Approximately 40% of patients were using oral corticosteroids at induction baseline. At maintenance baseline, oral corticosteroids other than budesonide and beclomethasone dipropionate were being used in 33.2% of patients in the placebo arm, 31.4% in the guselkumab 100 mg arm, and 36.3% in the guselkumab 200 mg arm. The mean daily prednisone-equivalent corticosteroid dosage was 17.3 mg/day, 15.0 mg/day, and 14.9 mg/day, respectively, at baseline, decreasing to 10.0 mg/day, 4.8 mg/day, and 4.6 mg/day, respectively, at week 44.

Among patients receiving oral corticosteroids at maintenance baseline, the majority of patients receiving guselkumab maintenance were able to eliminate corticosteroid use within 8 weeks (71.2% in the 100 mg arm and 65.8% in the 200 mg arm), compared with 36.0% in the placebo arm. Moreover, among the guselkumab-treated patients who attained week 44 CR (45.2% in the 100 mg arm and 50.0% in the 200 mg arm), 98.9% had not received corticosteroids for at least 12 weeks prior to week 44 (Figure 6). The CRs attained at week 44 of guselkumab maintenance occurred without the use of concomitant oral corticosteroids.

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Corticosteroid-Free Remission Through 3 Years of Upadacitinib Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Data From the Phase 3 Long-Term Extension Study U-ACTIVATE

The oral reversible JAK inhibitor upadacitinib demonstrated efficacy and tolerability as a corticosteroid-sparing treatment for patients with moderately to severely active UC in the U-ACHIEVE and U-ACCOMPLISH induction studies and the U-ACHIEVE maintenance study.[1] The U-ACTIVATE LTE study showed that upadacitinib maintenance achieved corticosteroid-free and symptomatic remissions through 48 weeks of treatment.[2] Dubinsky and colleagues reported updated results from the U-ACTIVATE study, showing rates of corticosteroid-free CR through week 96.[3]

The U-ACTIVATE LTE study enrolled patients with moderately to severely active UC who had a clinical response to 8 weeks of induction therapy with upadacitinib 45 mg once daily and completed the 52-week U-ACHIEVE maintenance study, in which they had received upadacitinib 15 mg or 30 mg. Rates of corticosteroid-free CR were evaluated through week 96 separately for patients who had maintained a stable dose of upadacitinib 15 mg or 30 mg during maintenance (UPA 15/15 or UPA 30/30) and for patients who initially received upadacitinib 15 mg and escalated to 30 mg at week 0 of the LTE after not achieving CR during the 52-week U-ACHIEVE maintenance study (UPA 15/30).

At week 96, among patients who had achieved a clinical response at week 0 of maintenance, the rate of corticosteroid-free CR per the adapted Mayo score was 78.5% in the UPA

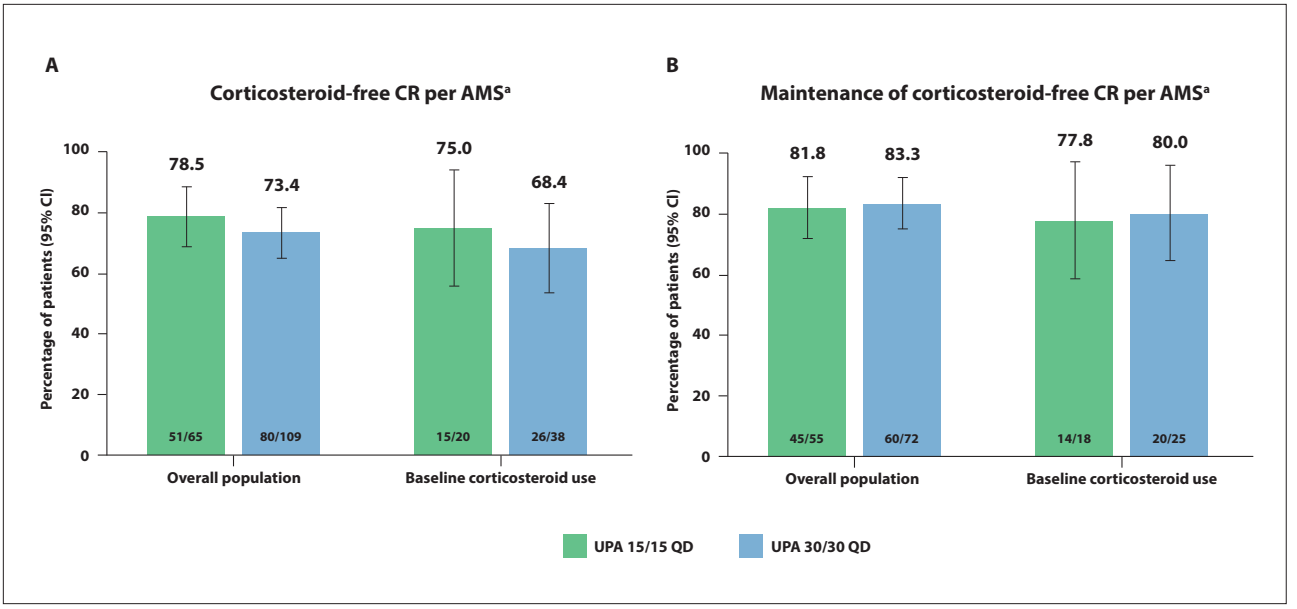

Figure 7. Clinical outcomes in patients with moderately to severely active ulcerative colitis at week 96 of the U-ACTIVATE long-term extension study by induction baseline corticosteroid use.

AMS, adapted Mayo score; CR, clinical remission; QD, once daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore; UPA, upadacitinib.

[a]CR per AMS: an AMS ≤2, with SFS ≤1 and not greater than baseline, RBS=0, and endoscopic subscore ≤1. AMS: the sum of the SFS, RBS, and endoscopic subscore.

Adapted from Dubinsky M, et al. Abstract P0849. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[3]

15/15 group (51/65) and 73.4% in the UPA 30/30 group (80/109) overall (Figure 7). In the subset of patients with baseline corticosteroid use at induction, rates of corticosteroid-free CR were 75.0% in the UPA 15/15 group (15/20) and 68.4% in the UPA 30/30 group (26/38).

Among the overall population (patients who had achieved a clinical response at week 0 of maintenance) who entered the LTE, the majority of corticosteroid-free CRs were sustained at week 96. Rates of maintained corticosteroid-free CR at week 96 were 81.8% in the UPA 15/15 group (45/55) and 83.3% in the UPA 30/30 group (60/72) overall. In the subset of patients with baseline corticosteroid use at induction, rates of corticosteroid-free CR were 77.8% in the UPA 15/15 group (14/18) and 80.0% in the UPA 30/30 group (20/25).

Of the 20 patients who entered the LTE in the UPA 15/30 group, 80% (16/20) attained corticosteroid-free CR and 100% (3/3) maintained

Upadacitinib was superior to placebo across clinical, endoscopic, and histologic endpoints; was effective in achieving corticosteroid-sparing treatment; and was well tolerated in the U-ACHIEVE maintenance study. In the U-ACTIVATE LTE trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical program, corticosteroid-free and symptomatic remission was achieved with upadacitinib maintenance treatment and was maintained in more than 80% of patients through 48 weeks. Patients from the LTE study were further assessed up to 96 weeks. Most of these patients achieved and maintained corticosteroid-free CR, suggesting that upadacitinib continues to have a persistent benefit, is an excellent long-term treatment option for moderately to severely active UC, and can spare patients from corticosteroid use.

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corticosteroid-free CR. Of the 7 patients with corticosteroid use at baseline who entered the LTE in the UPA 15/30 group, 71.4% (5/7) achieved a corticosteroid-free CR at week 96 and 100% (2/2) maintained a corticosteroid-free CR at Week 96.

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3. Dubinsky M, Atreya R, Nakase H, et al. Corticosteroid-free remission through 3 years of upadacitinib therapy in patients with moderately to severely active ulcerative colitis: data from the phase 3 LTE study U-ACTIVATE. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P0849.

ABSTRACT SUMMARY Delayed Response to Ozanimod in Patients with Moderate vs Severe Endoscopic Disease: 4-Year Interim Analysis of the True North Open-Label Extension Study

The impact of baseline endoscopic disease activity on the likelihood of attaining delayed responses to ozanimod was assessed during the True North OLE study (Abstract P4346). In the True North study, 28% of patients (n=226) did not attain a response to induction ozanimod and entered the OLE for extended induction. Of these patients, 70.4% had severe endoscopic disease at baseline (Mayo endoscopic subscore [MES] of 3), and the remaining 29.6% had moderate activity (MES of 2). Response rates were higher in moderate-UC vs severe-UC patients at OLE week 5 (66.2% vs 47.9%) and week 10 (67.2% vs 59.4%). However, at week 190, the symptomatic response rate reached 89.5% for moderate-UC and 89.4% for severe-UC patients, suggesting that patients with severe UC require longer exposure to achieve similar efficacy, but both groups ultimately attain durable responses. Mucosal efficacy was also durable through week 190, with similar rates reported in both groups.

Histologic and Combined Histologic and Endoscopic Outcomes After Guselkumab Maintenance Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Week 44 Results From the Phase 3 QUASAR Maintenance Study

Panés and colleagues conducted an analysis that evaluated histologic and combined histologic and endoscopic outcomes with guselkumab maintenance in patients with a clinical response to IV guselkumab induction.[1] For each of the parameters assessed, rates of improvement or remission were significantly higher with either of the 2 guselkumab regimens than with placebo (guselkumab withdrawal) (P<.001 for each).

Specifically, histologic improvement, defined as a Geboes score of 3.1 or higher (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue), was attained at week 44 in 64.9% of patients receiving maintenance SC guselkumab 100 mg SC every 8 weeks, 64.2% of patients receiving maintenance guselkumab 200 mg SC every 4 weeks, and 30.5% of patients

Clinically meaningful improvements in endoscopic and histologic outcomes compared with placebo (guselkumab withdrawal) were notably present in both the biologic/JAK inhibitor–naive patient subpopulation and also in the patients who had an inadequate response or intolerance to biologics and/or JAK inhibitors. As expected, patients who received placebo after responding to initial therapy had progressive worsening of histologic and combined histologic and endoscopic outcomes. The findings of this study have important clinical implications for patient care.

—Gary R. Lichtenstein, MD

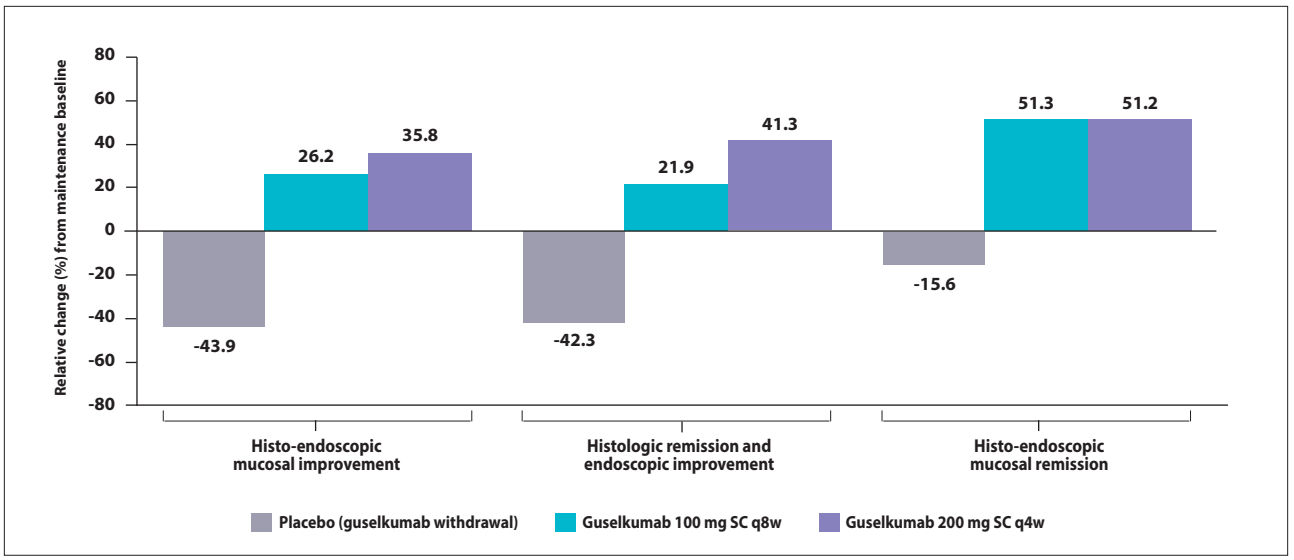

Figure 8. Relative change in combined histologic/endoscopic outcomes from maintenance baseline to week 44 for patients with moderately to severely active ulcerative colitis randomized to receive guselkumab vs placebo in the QUASAR maintenance study. q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous.
Adapted from Panés J, et al. Abstract P4352. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[1]

receiving maintenance placebo. Rates of histologic remission, defined as a Geboes score of 2 or higher (absence of neutrophils from the mucosa, no crypt destruction, and no erosions, ulcerations, or granulation tissue), at week 44 were 59.0% with guselkumab 100 mg, 60.5% with guselkumab 200 mg, and 26.8% with placebo.

Rates of histo-endoscopic mucosal improvement, defined as a Geboes score 3.1 or higher and Mayo endoscopic subscore of 0 or 1 with no friability, at week 44 were 43.6% with guselkumab 100 mg, 47.9% with guselkumab 200 mg, and 16.8% with placebo. Rates of histologic remission and endoscopic improvement, defined as a Geboes score of 2 or higher and Mayo endoscopic subscore of 0 or 1 with no friability, at week 44 were 41.5% with guselkumab 100 mg, 46.8% with guselkumab 200 mg, and 15.8% with placebo. Rates of histo-endoscopic mucosal remission, defined as a Geboes score of 2 or higher and Mayo endoscopic subscore of 0, at week 44 were 31.4% with guselkumab 100 mg, 32.6% with guselkumab 200 mg, and 14.2% with placebo.

Rates of each histologic and combined histologic/endoscopic outcome at week 44 were also significantly higher with guselkumab over placebo regardless of patients' history of biologic/JAK inhibitor use.

Changes in the combined histologic/endoscopic outcomes were noted from maintenance baseline to week 44 between patients randomized to receive guselkumab vs placebo (Figure 8). Across the outcomes assessed (histo-endoscopic mucosal improvement, histologic remission and endoscopic improvement, and histo-endoscopic mucosal remission), the proportion of patients achieving each outcome increased in the guselkumab arms but decreased in the placebo arm.

Reference

1. Panés J, Dignass A, Hisamatsu T, et al. Histologic and combined histologic and endoscopic outcomes after guselkumab maintenance therapy in patients with moderately to severely active ulcerative colitis: week 44 results from the phase 3 QUASAR maintenance study. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P4352.

ABSTRACT SUMMARY Efficacy and Safety of Etrasimod in Patients With Ulcerative Colitis Stratified by Body Mass Index: A Post Hoc Analysis From the ELEVATE UC Clinical Program

An analysis of the ELEVATE UC clinical program reported on the impact of body mass index (BMI) on the efficacy and safety of etrasimod (Abstract P4336). A total of 787 patients were stratified by baseline BMI into lower than 25 (56.3%), 25 to 30 (27.6%), and higher than 30 (16.1%) and assigned to placebo or etrasimod 2 mg once daily. Across BMI subgroups, etrasimod was associated with superior efficacy over placebo at week 12 and at week 52, except for clinical remission rate in the subgroup with BMI higher than 30 at week 12. The rate of corticosteroid-free CR at week 52 was also significantly higher with etrasimod vs placebo in all 3 BMI subgroups. In the safety analysis, the incidence of TEAEs and serious AEs was generally consistent regardless of BMI subgroup, as was the incidence of AEs requiring treatment discontinuation.

Safety of Long-Term Ozanimod Treatment Up to 5 Years in Patients With Moderately to Severely Active Ulcerative Colitis: An Interim Analysis of the True North Open-Label Extension

Ozanimod is a selective sphingosine-1 phosphate (S1P) receptor modulator that is FDA-approved for the treatment of moderately to severely active UC in adults based on results of the phase 3 True North study, in which ozanimod demonstrated superior efficacy over placebo and acceptable tolerability for up to 52 weeks as induction and maintenance therapy.[1,2] Ozanimod continues to be evaluated in the True North open-label extension (OLE) study, in which patients receive ozanimod 0.92 mg orally once daily.

Abraham and colleagues reported on the long-term safety of ozanimod in the True North and True North OLE studies, after a total treatment period of up to approximately 5 years.[3] The analysis includes 823 patients who entered the OLE, including patients who did not achieve clinical response at True North week 10, patients who lost response during maintenance, and patients who completed maintenance at True North week 52. At the data cutoff, all patients had either completed week 190 of the OLE (43%) or had already discontinued the study (57%); the total ozanimod exposure was 2681 person-years (PY).

The most frequent reasons for discontinuation reported by patients

> In the True North Study, which assessed ozanimod vs placebo, it is comforting to see that no new safety concerns were identified. A significant number of patients (43%) persisted on medication for up to 5 years. The rate of treatment discontinuation owing to AEs was low. With 2681 PY of follow-up, the study has not yet achieved adequate power to assess for the presence of uncommon events such as lymphoma. Continued follow-up will be necessary.
>
> —Gary R. Lichtenstein, MD

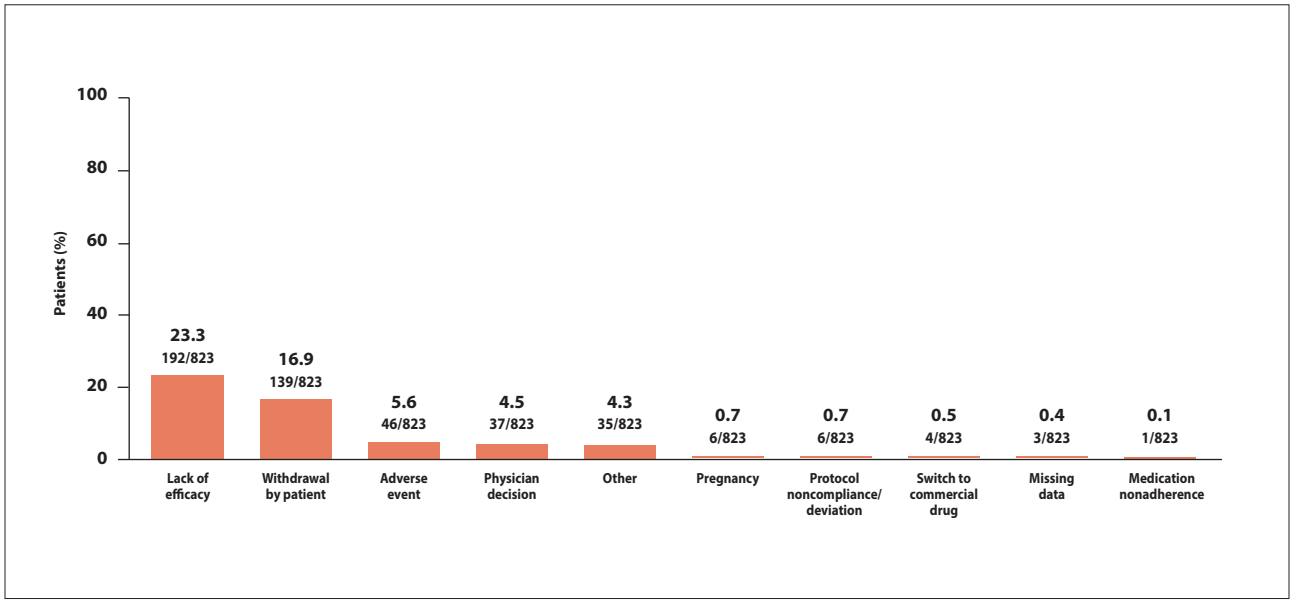

Figure 9. Primary reasons for discontinuation of ozanimod up to week 190 in patients with moderately to severely active ulcerative colitis in the True North open-label extension study.

Adapted from Abraham BP, et al. Abstract P4381. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[3]

ABSTRACT SUMMARY Long-Term Outcomes of an Infliximab-First vs Vedolizumab-First Treatment Strategy in Biologic-Naive Patients With Ulcerative Colitis

A retrospective observational study was presented comparing outcomes after 30 months among biologic-naive patients with UC receiving infliximab or vedolizumab as their first-line biologic (Abstract P0957). The single-center analysis included 144 patients who had received infliximab first (n=72) or vedolizumab first (n=72), matched 1:1 using cardinality matching. No significant differences were noted between the 2 groups in the inflammatory bowel disease–related hospitalization incident rate (incident rate ratio [IRR], 1.978; 95% CI, 0.641-6.107), corticosteroid courses (IRR, 0.664; 95% CI, 0.384-1.146), or medication switches (IRR, 1.08; 95% CI, 0.415-2.809). The risk of serious infections was increased in patients who received infliximab first; however, this did not extend to an increased incidence of serious infections over 30 months. At 30 months, CR rates in the infliximab-first and vedolizumab-first groups were 69.4% and 76.4%, respectively (*P*=.453), and endoscopic remission rates were 55.6% and 65.3%, respectively (*P*=.359). Overall, 23.6% of the infliximab-first group and 25.0% of the vedolizumab-first group switched to 1 additional biologic; 9.7% and 8.3%, respectively, switched to at least 2 different biologics. The investigators concluded that starting with either infliximab or vedolizumab is effective and safe for most patients with UC.

up to OLE week 190 were lack of efficacy (23.3%) and withdrawal by patient (16.9%); 5.6% of patients discontinued owing to AEs (Figure 9). Investigators reported that most treatment-emergent AEs (TEAEs) had not changed with an additional year of ozanimod exposure since the last analysis, reported in early 2024 after up to 4 years of treatment.[4]

The safety profile was consistent with prior reports, and no new safety issues were identified. The most frequent TEAEs were lymphopenia (exposure-adjusted incidence rate [EAIR], 5.8/100 PY), anemia (EAIR, 3.6/100 PY), lymphocyte count decreased (EAIR, 3.6/100 PY), alanine aminotransferase increased (3.2/100 PY), arthralgia (EAIR, 3.0/100 PY), headache (EAIR, 2.6/100 PY), gamma-glutamyl transferase increased (EAIR, 2.3/100 PY), and hypertension (EAIR, 2.2/100 PY).

The most frequent infections were COVID-19 (EAIR, 4.1/100 PY), nasopharyngitis (EAIR, 3.6/100 PY), upper respiratory tract infection (EAIR, 2.3/100 PY), serious infection (EAIR, 1.7/100 PY), herpes zoster (EAIR, 1.2/100 PY), and sinusitis (EAIR, 1.2/100 PY). No cases of progressive multifocal leukoencephalopathy were reported. Reductions in absolute lymphocyte count (ALC) to less than 500 cells/mm^3 occurred in 57.2% of patients overall, but only 6.6% had ALC reductions to less than 200 cells/mm^3. Reductions in ALC to less than 200 cells/mm^3 did not appear to be temporally associated with serious or opportunistic infections. The investigators concluded that long-term ozanimod treatment, up to approximately 5 years, continues to be well tolerated in patients with moderately to severely active UC.

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