GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

July 2023 Volume 19, Issue 7, Supplement 3

A SPECIAL MEETING REVIEW EDITION

Highlights in Ulcerative Colitis From Digestive Disease Week 2023

A Review of Selected Presentations From DDW 2023
• May 6-9, 2023 • Chicago, Illinois

Special Reporting on:

- Long-Term Safety of 3 Years of Ozanimod in Moderately to Severely Active Ulcerative Colitis: An Interim Analysis of the True North Open-Label Extension
- Real-World Effectiveness and Safety of Ozanimod: 1-Year Follow-up From a Large Tertiary Center
- Analyses From the Phase 3 True North Study of Ozanimod in Ulcerative Colitis Patients
- Real-World Comparison of Effectiveness Between Tofacitinib and Ustekinumab in Patients With Ulcerative Colitis Exposed to at Least One Anti-TNF Agent: Results From the TORUS Study
- Infliximab Clearance in Relation to Disease Activity During Induction and Maintenance Therapy of Acute Severe and Ambulatory Pediatric Ulcerative Colitis
- PK, Efficacy, and Safety of Mirikizumab as Induction Therapy in Pediatric Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 2 SHINE-1 Study
- The Efficacy and Safety of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 QUASAR Induction Study
- Etrasimod for the Treatment of Ulcerative Colitis: Up to 2.5 Years of Pooled Safety Data From Global Clinical Trials
- Withdrawal Versus Continuation of Thiopurine in Vedolizumab-Treated Patients With Ulcerative Colitis (VIEWS): A Multi-Centre Randomised Controlled Trial

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Stephen B. Hanauer, MD
Professor of Medicine
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

ON THE WEB:
gastroenterologyandhepatology.net

Indexed through the National Library of Medicine
(PubMed/Medline), PubMed Central (PMC), and EMBASE

EDITORIAL ADVISORY BOARD

Long-Term Safety of 3 Years of Ozanimod in Moderately to Severely Active Ulcerative Colitis: An Interim Analysis of the True North Open-Label Extension

Ozanimod is a selective modulator of the sphingosine-1-phosphate (S1P) receptor. The drug is approved for the treatment of moderately to severely active ulcerative colitis (UC) and has demonstrated a favorable safety profile in UC as well as in multiple sclerosis.[1] The phase 3 True North study evaluated ozanimod vs placebo in patients with moderately to severely active UC.[2] The study included a 10-week induction phase, a 42-week maintenance phase, and a 94-week open-label extension (OLE) study. For induction, 645 patients in cohort 1 were randomized 2:1 to receive placebo or ozanimod (0.92 mg, daily), while 367 patients in cohort 2 received open-label ozanimod (0.92 mg, daily). At week 10, patients in the placebo arm who exhibited a response continued with placebo (n=69). Responding patients in either cohort 1 or cohort 2 who received induction treatment with ozanimod were evenly randomized to receive placebo (n=227) or continue with ozanimod (n=230). The OLE study included patients who did not respond to induction, patients who lost a response in the maintenance phase, and patients who completed the maintenance phase.

In comparison with placebo, ozanimod demonstrated efficacy in both the induction and maintenance phases of the True North study. At week 10, ozanimod was superior to placebo in respect to clinical remission (18.4% vs 6.0%), clinical response (47.8% vs 25.9%), endoscopic improvement (27.3% vs 11.6%), and mucosal healing (12.6% vs 3.7%). Similarly, at week 52, outcomes were superior with ozanimod vs placebo, including clinical remission (37.0% vs 18.5%), clinical response (60.0% vs 41.0%), endoscopic improvement (45.7% vs 26.4%), mucosal healing (29.6% vs 14.1%), and others. Prior analyses of data from the True North OLE have shown a favorable safety profile in 131 patients with UC treated with ozanimod for up to 146 weeks.[3]

An interim analysis evaluated the cumulative long-term safety of ozanimod in all patients who entered the True North OLE study.[4] This group of 823 patients represented 2219 patient-years of exposure to ozanimod, with a mean duration of exposure of 2.7 ± 1.6 years per patient. Patients in this analysis had a mean age of 41.7 ± 13.6 years, and 59.3% were male. The mean age at UC diagnosis was 34.5 ± 13.3 years, and the mean time since UC diagnosis was 7.4 ± 7.0 years. At screening, 32% of the patients were using corticosteroids. The exposure-adjusted incident rate per 100 patient-years ($EAIR_{100}$) was 87.6 for treatment-emergent adverse events (AEs) in 672 patients (81.7%), 7.4 for serious treatment-emergent AEs in 149 patients (18.1%), and 2.5 for treatment-emergent AEs leading to discontinuation of ozanimod in 55 patients (6.7%). The most frequent treatment-emergent AEs included lymphopenia ($EAIR_{100}$, 6.4) in 128 patients (15.6%), anemia ($EAIR_{100}$, 4.2) in 86 patients (10.4%), and nasopharyngitis ($EAIR_{100}$, 4.1) in 85 patients (10.3%). The most common infections included serious infection in 41 patients (5.0%; $EAIR_{100}$, 1.9), nasopharyngitis in 85 patients (10.3%; $EAIR_{100}$, 4.1), COVID-19 in 66 patients (8.0%; $EAIR_{100}$, 3.0), and upper respiratory tract infection in 56

Table 1. The Most Frequent TEAEs for All Patients Who Entered the OLE From TN

	All TN Patients Enrolled in the OLE (N=823)
Adverse Event	**n (%)**
TEAEs	672 (81.7)
Serious TEAEs	149 (18.1)
TEAEs leading to treatment discontinuation	55 (6.7)
Most frequent TEAEs (occurring in ≥5% of patients)	
• Lymphopenia	128 (15.6)
• Anemia	86 (10.4)
• Nasopharyngitis	85 (10.3)
• Decreased lymphocyte count	84 (10.2)
• Increased alanine aminotransferase	74 (9.0)
• Arthralgia	74 (9.0)
• COVID-19	66 (8.0)
• Headache	63 (7.7)
• Upper respiratory tract infection	56 (6.8)
• Increased γ-glutamyl transferase	54 (6.6)
• Hypertension	49 (6.0)
• UC exacerbation	44 (5.3)
• Cough	42 (5.1)

OLE, open-label extension; TEAE, treatment-emergent adverse event; TN, True North; UC, ulcerative colitis.
Adapted from Abreu et al. Abstract 950. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[4]

patients (6.8%; $EAIR_{100}$, 2.7; Table 1). The most common malignancy was basal cell carcinoma ($EAIR_{100}$, 0.3), followed by prostate cancer, colon adenocarcinoma, breast cancer, rectal adenocarcinoma, and rectal cancer stage II, each of which had an $EAIR_{100}$ of 0.1. AEs of special interest included hypertension ($EAIR_{100}$, 2.3), macular edema ($EAIR_{100}$, 0.2), bradycardia ($EAIR_{100}$, 0.1), and third-degree atrioventricular block ($EAIR_{100}$, 0.1). The $EAIR_{100}$ for opportunistic infection was 1.5. An absolute lymphocyte count below 200/mm^3 was observed in 7.8% of patients in the analysis and was not associated with an increased rate of opportunistic infections.

References

1. Zeposia [ozanimod] prescribing information. Bristol Myers Squibb. Princeton, NJ; 2022.
2. Sandborn WJ, Feagan BG, D'Haens G, et al; True North Study Group. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2021;385(14):1280-1291.
3. Danese S, Abreu MT, Wolf DC, et al. Efficacy and safety of 3 years of continuous ozanimod treatment: an interim analysis of the True North open-label extension study. Abstract DOP37. Presented at: 18th Congress of ECCO; March 1-4, 2023; Copenhagen, Denmark.
4. Abreu MT, Danese S, Wolf DC, et al. Long-term safety of 3 years of ozanimod in moderately to severely active ulcerative colitis: an interim analysis of the True North open-label extension. Abstract 950. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.

Real-World Effectiveness and Safety of Ozanimod: 1-Year Follow-up From a Large Tertiary Center

Real-world data pertaining to ozanimod outcomes in patients with UC are limited. To address this knowledge gap, a real-world study of ozanimod in patients with UC was conducted.[1] The prospective, observational cohort study included consecutive patients treated with ozanimod at a single center. Patients were followed for up to 1 year. Clinical response was defined as a decrease from baseline of at least 3 points in the Simple Clinical Colitis Activity Index (SCCAI) score. Clinical remission was defined as an SCCAI score of 2 or lower.

Among the 45 included patients, 34 had clinically active disease at enrollment; 11 patients were in clinical remission but had active disease by endoscopy. Patients had a median age of 35 years and a median duration of disease of 6 years; 58% were male, 51% had extensive colitis, and 29% were on corticosteroid therapy at baseline. At week 10 of ozanimod therapy, among the patients who had clinically active disease at baseline, the rate of clinical response was 58% and the rate of clinical remission was 48%. At week 52, among 24 patients, the rate of clinical response as well as of clinical remission was 29%. Rates of relapse-free survival were similar regardless of exposure to prior advanced therapy, including when stratified by the number of prior advanced therapies and specifically in patients with prior exposure to vedolizumab. An AE of any grade was experienced by 13 patients, and 2 patients with AEs required discontinuation of ozanimod: hypertensive crisis in 1 patient with a history of hypertension and fatigue in 1 patient. Both AEs resolved after drug discontinuation. Symptomatic bradycardia was not observed.

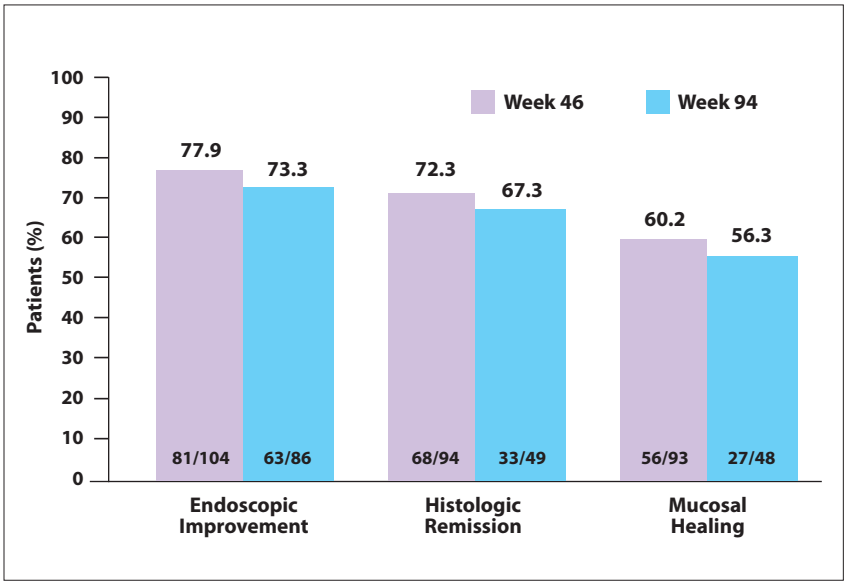

Figure 1. The efficacy of ozanimod at OLE weeks 46 and 94 in patients with a clinical response at OLE entry at week 52 (98 and 146 weeks of continuous treatment, respectively; OC analysis). OC, observed case; OLE, open-label extension. Adapted from Abreu et al. Abstract Tu1725. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[2]

Another interim analysis was conducted of 131 patients in the True North trial who received continuous ozanimod during the induction and maintenance phases, achieved a clinical response at week 52, and were enrolled in the OLE study.[2,3] Endoscopic improvement was defined as an endoscopy subscore of 1 or lower, histologic remission as a Geboes score of less than 2, and mucosal healing as an endoscopy subscore of 1 or lower and a Geboes score of less than 2. Data were evaluated by observed case analysis and nonresponder imputation analysis. There were 94 patients (72%) who completed the induction, maintenance, and OLE portions of the study. The 131 patients had a median age of 44.3 years, and 51.9% were female. The mean age at diagnosis was 36.1 ±

13.4 years, the mean time since diagnosis was 8.5 ± 7.3 years, and 32.1% had extensive UC. Of the 131 patients who demonstrated a clinical response at week 52, most achieved endoscopic improvement (77.9% and 73.3%), histologic remission (72.3% and 67.3%), and mucosal healing (60.2% and 56.3%) at OLE weeks 46 and 94, respectively (Figure 1). Ozanimod therapy was associated with a reduction in the mean Mayo endoscopic subscore from 2.5 ± 0.5 at baseline to 1.0 ± 0.9 at OLE week 52, to 0.9 ± 0.9 at OLE week 46, and to 1.0 ± 1.0 at OLE week 94. The data suggest that long-term ozanimod therapy yields sustained endoscopic and histologic improvement in patients with moderately to severely active UC.

References

1. Cohen NA, Choi D, Garcia NM, et al. Real world effectiveness and safety of ozanimod: one-year follow-up from a large tertiary center. Abstract Tu1803. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
2. Abreu MT, Danese S, Wolf DC, et al. Effects of ozanimod on histologic remission and mucosal healing over 3 years of continuous treatment in patients with ulcerative colitis. Abstract Tu1725. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
3. Sandborn WJ, Feagan BG, D'Haens G, et al; True North Study Group. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2021;385(14):1280-1291.

Analyses From the Phase 3 True North Study of Ozanimod in Ulcerative Colitis Patients

Of patients who failed to achieve a response at week 10 of induction in the True North trial, 50% achieved symptomatic clinical response with further ozanimod therapy in the OLE study.[1,2] A related analysis evaluated outcomes at approximately 2 years in 226 patients from cohorts 1 and 2 who did not exhibit a response after 10 weeks of ozanimod induction therapy and then entered the OLE study.[3] Patients had a mean age of 39.6 ± 13.6 years, and 67.3% were male. The mean age at diagnosis was 33.2 ± 13.2 years, and the mean time since UC diagnosis was 6.6 ± 6.3 years. At OLE weeks 46 and 94, ozanimod therapy was associated with clinical response rates of 62.4% and 73.8%, clinical remission rates of 26.0% and 35.3%, and rates of corticosteroid-free remission of 23.6% and 32.9%, respectively. At week 5 of the OLE study, on the basis of observed case analysis, 53.6% of patients had achieved a symptomatic clinical response, and this percentage rose to 86.3% at OLE week 94 (Figure 2). Symptomatic clinical remission was noted in 17.1% of patients at OLE week 5, and the percentage rose to 57.9% at OLE week 94. Mean total Mayo scores decreased from 9.2 at baseline to 3.8 at OLE week 94, and continuous reductions in mean partial Mayo scores were observed from

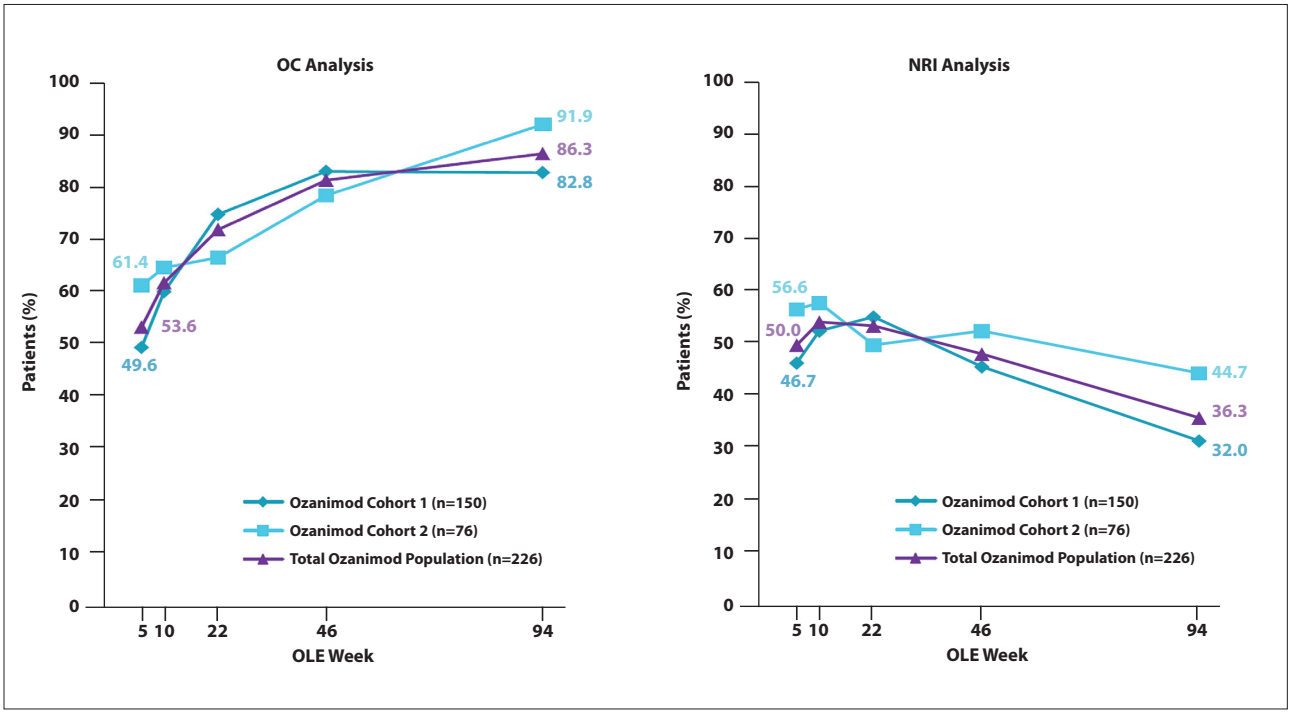

Figure 2. Symptomatic clinical response in nonresponders who entered the OLE after 10 weeks in TN: OC and NRI analyses. NRI, nonresponder imputation; OC, observed case; OLE, open-label extension; TN, True North. Adapted from Rubin et al. Abstract Tu1736. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[3]

baseline through OLE week 94.

Data from the same True North population of 226 patients with UC were evaluated to determine endoscopic and histologic endpoints.[4] The analysis included 150 patients in cohort 1 and 76 patients in cohort 2. At weeks 46 and 94, on the basis of observed case analysis, ozanimod therapy was associated with endoscopic improvement in 29.9% vs 47.7%, histologic remission in 42.0% vs 48.4%, and mucosal healing in 24.4% vs 39.1% of the 226 patients, respectively. Outcomes were generally similar in patients from cohort 1 and cohort 2.

A third study evaluated outcomes in 77 True North patients who responded to ozanimod therapy during the induction phase, were randomized to placebo for the maintenance phase, experienced relapse, and were started again on ozanimod therapy during the OLE study.[5] By the time of data cutoff, 49 patients (31.2%) had withdrawn from OLE treatment, mostly because of lack of efficacy. On the basis of observed case analysis, at OLE weeks 46 and 94, rates of endoscopic improvement were 50.0% and 60.0%, rates of histologic remission were 55.8% and 67.9%, and rates of mucosal healing were 41.9% and 48.1%, respectively.

References

1. Sandborn WJ, Feagan BG, D'Haens G, et al; True North Study Group. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2021;385(14):1280-1291.
2. Panaccione R, Afzali A, Hudesman D, et al. Extended therapy with ozanimod for delayed responders to ozanimod in moderately to severely active ulcerative colitis: data from the True North open-label extension study. Abstract OP196. Presented at: 30th United European Gastroenterology Week; October 8-11, 2022; Vienna, Austria.
3. Rubin DT, Colombel JF, Chiorean MV, et al. Extended induction in the True North open-label extension study: clinical outcomes of ~2 years of ozanimod treatment. Abstract Tu1736. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
4. Chiorean MV, Colombel JF, Rubin DT, et al. Achievement and maintenance of endoscopic, histologic, and combined outcomes after extended induction in week 10 nonresponders of ozanimod: 2-year interim analysis of the True North open-label extension study. Abstract Tu1745. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
5. Regueiro MD, Dignass A, Colombel JF, et al. Endoscopic, histologic, and combined outcomes with reinitiation of ozanimod after temporary discontinuation: 2-year interim analysis of the True North open-label extension study. Abstract Tu1742. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.

Real-World Comparison of Effectiveness Between Tofacitinib and Ustekinumab in Patients With Ulcerative Colitis Exposed to at Least One Anti-TNF Agent: Results From the TORUS Study

Tofacitinib is an inhibitor of Janus kinase, and ustekinumab is an inhibitor of interleukin 12 (IL-12) and IL-23. The TORUS study compared tofacitinib with ustekinumab in patients with UC and prior exposure to at least one anti–tumor necrosis factor (TNF) agent.[1] The main objectives of this retrospective, multicenter study were to determine the short- and long-term efficacy of the agents, both of which are approved for the treatment of UC. Included patients were adults with symptomatic UC, indicated by a partial Mayo score higher than 2. Patients had begun treatment with tofacitinib or ustekinumab between January 2019 and June 2022, and all patients had previously received therapy with at least one anti-TNF agent. Patients with acute severe colitis or prior colectomy were excluded. The primary endpoint was corticosteroid-free remission at week 16, on the basis of a composite of corticosteroid-free clinical remission and a Mayo endoscopic score of 0 or 1.

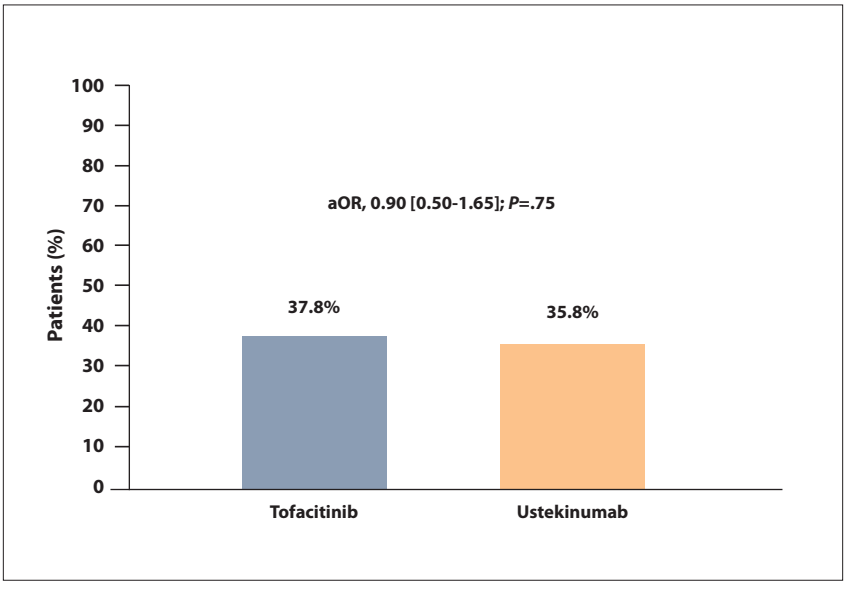

Figure 3. The rate of corticosteroid-free remission at week 16 after propensity score analysis. aOR, adjusted odds ratio. Adapted from Buisson et al. Abstract 14. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[1]

The analysis included 124 patients treated with tofacitinib and 165 treated with ustekinumab. Baseline characteristics were well balanced between the 2 groups. However, more patients in the tofacitinib group had extensive disease (55.7% vs 42.4%; *P*=.03), and patients in the tofacitinib group were more likely to have pancolitis (55.6% vs 42.4%; *P*=.026). In the tofacitinib group, 18.7% of patients

had received prior ustekinumab, and in the ustekinumab group, 26.2% had received prior ustekinumab. Between 25% and 30% of patients were using corticosteroids at baseline. At week 16, the proportions of patients who met the primary endpoint of corticosteroid-free remission were 37.8% with tofacitinib and 35.8% with ustekinumab (adjusted odds ratio [OR], 0.90; 95% CI, 0.50-1.65; *P*=.75; Figure 3). The rates of endoscopic improvement were 17.0% with tofacitinib and 11.7% with ustekinumab (adjusted OR, 0.64; 95% CI, 0.27-1.53; *P*=.32). The rates of mucosal healing, defined as a composite of steroid-free clinical remission, endoscopic improvement, and histologic healing, were also similar with tofacitinib and ustekinumab (4.4% vs 7.8%; adjusted OR, 0.64; 95% CI, 0.27-1.53; *P*=.32).

Subgroup outcomes were evaluated after propensity score analysis. Patients who had received treatment with 3 or more prior biologic therapies were more likely to achieve corticosteroid-free remission at week 16 with tofacitinib than with ustekinumab. Predictors of failure with ustekinumab included primary failure with 1 or more biologic therapies (OR, 2.88; 95% CI, 1.20-6.98) and exposure to 3 or more biologics (OR, 2.45; 95% CI, 1.03-5.82). The rates of long-term secondary loss of response were similar for the 2 groups (adjusted hazard ratio, 0.53; 95% CI, 0.16-1.74; *P*=.30).

Reference

1. Buisson A, Serrero M, Altwegg R, et al. Real-world comparison of effectiveness between tofacitinib and ustekinumab in patients with UC exposed to at least one anti-TNF agent: result from the TORUS study. Abstract 14. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.

Infliximab Clearance in Relation to Disease Activity During Induction and Maintenance Therapy of Acute Severe and Ambulatory Pediatric Ulcerative Colitis

Infliximab, an inhibitor of TNF, is the standard of care for pediatric patients at least 6 years of age who have corticosteroid-refractory UC or are unable to maintain corticosteroid-free remission on mesalamine.[1,2] However, fewer than 40% of patients achieve clinical remission after treatment with the recommended infliximab dosing regimen. Higher infliximab clearance rates may lead to suboptimal therapy, especially in patients with acute UC. To explore this possibility, a prospective study was conducted at 8 centers to determine whether infliximab clearance rates were higher in pediatric patients initially hospitalized with acute severe UC than in patients with less-severe UC.[3,4]

The study included 37 patients with acute severe UC and 15 with ambulatory UC. In the group with acute severe UC, the median age of the patients was 14.3 years, and 48.6% were female. Extensive disease and/or pancolitis was noted in 91.9% of the patients, and the mean baseline Pediatric Ulcerative Colitis Activity Index (PUCAI) score was 65. Patients received a median initial dose of infliximab of 9.9 mg/kg. In the ambulatory population, the median age was 15.0 years, and 46.6% of the patients were female. Extensive disease and/or pancolitis was observed in 92.9% of patients, and the mean baseline PUCAI score was 10. Patients in the ambulatory UC group received a median initial dose of infliximab of 5 mg. Predicted infliximab clearance was higher in the acute severe UC cohort than in the ambulatory cohort (*P*<.01; Figure 4). Modeling also predicted a decrease in infliximab clearance over time.

Multivariable linear mixed effects modeling was performed to determine independent variables associated with infliximab clearance at various times from week 0 to week 26 of treatment.

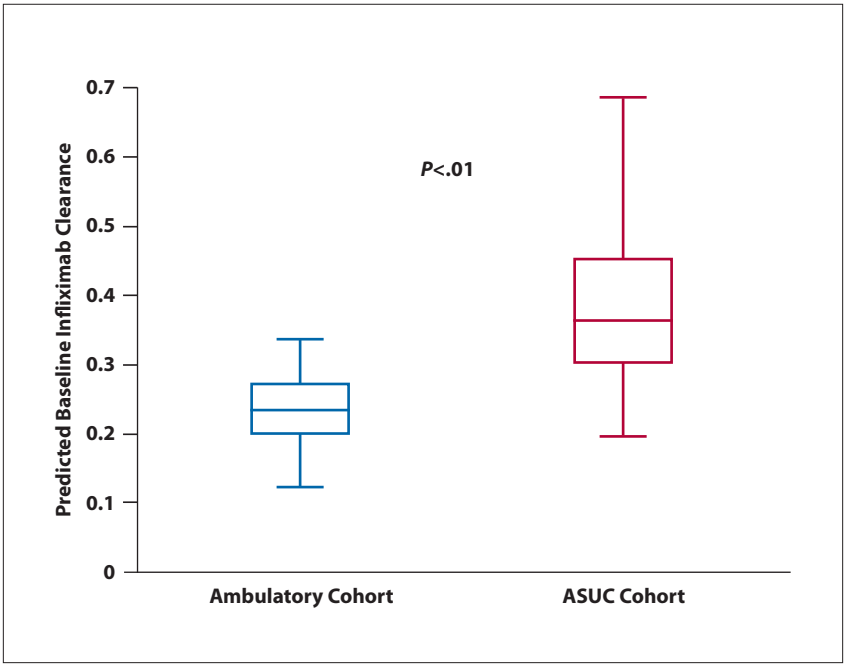

Figure 4. The predicted infliximab clearance in the ASUC and the ambulatory cohorts. ASUC, acute severe ulcerative colitis. Adapted from Rosen et al. Abstract 714. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[3]

Analyses were conducted with pooled data from week 0 to 2, week 2 to 4, week 4 to 8, week 8 to 15, and week 15 to 26. For all times from week 0 to week 15, the infliximab clearance rate was higher in patients whose PUCAI score was 35 or higher, indicating moderately to severely active UC, than in patients whose PUCAI score was 30 or lower, indicating quiescent or mild disease. By weeks 15 to 26, the infliximab clearance rates were similar for the PUCAI subgroups.

References

1. Hyams J, Damaraju L, Blank M, et al; T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2012;10(4):391-399.
2. Remicade [infliximab] prescribing information. Janssen Biotech; Horsham, PA. 2021.
3. Rosen MJ, Rabizadeh S, Panetta JC, et al. Infliximab clearance in relation to disease activity during induction and maintenance therapy of acute severe and ambulatory pediatric ulcerative colitis. Abstract 714. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
4. Whaley KG, Xiong Y, Karns R, et al. Multicenter cohort study of infliximab pharmacokinetics and therapy response in pediatric acute severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2023;21(5):1338-1347.

PK, Efficacy, and Safety of Mirikizumab as Induction Therapy in Pediatric Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 2 SHINE-1 Study

Mirikizumab is a humanized antibody that binds to the p19 subunit of IL-23, a key inflammatory agent in inflammatory bowel disease.[1] The open-label, multicenter, phase 2 SHINE-1 study evaluated the pharmacokinetics, efficacy, and safety of mirikizumab in pediatric patients with moderately to severely active UC.[2] Eligible patients were between 2 and less than 18 years of age and weighed more than 10 kg. Patients had an established diagnosis of UC for at least 3 months before baseline and moderately to severely active UC for 14 days before baseline. Enrolled patients also had exhibited an inadequate response, loss of response, or inability to tolerate treatment with at least one corticosteroid, immunomodulator, biologic therapy, or Janus kinase inhibitor for their UC. After 12 weeks of induction therapy, patients continued open-label maintenance therapy with mirikizumab. The primary objective was to determine the pharmacokinetics of mirikizumab in the pediatric patient

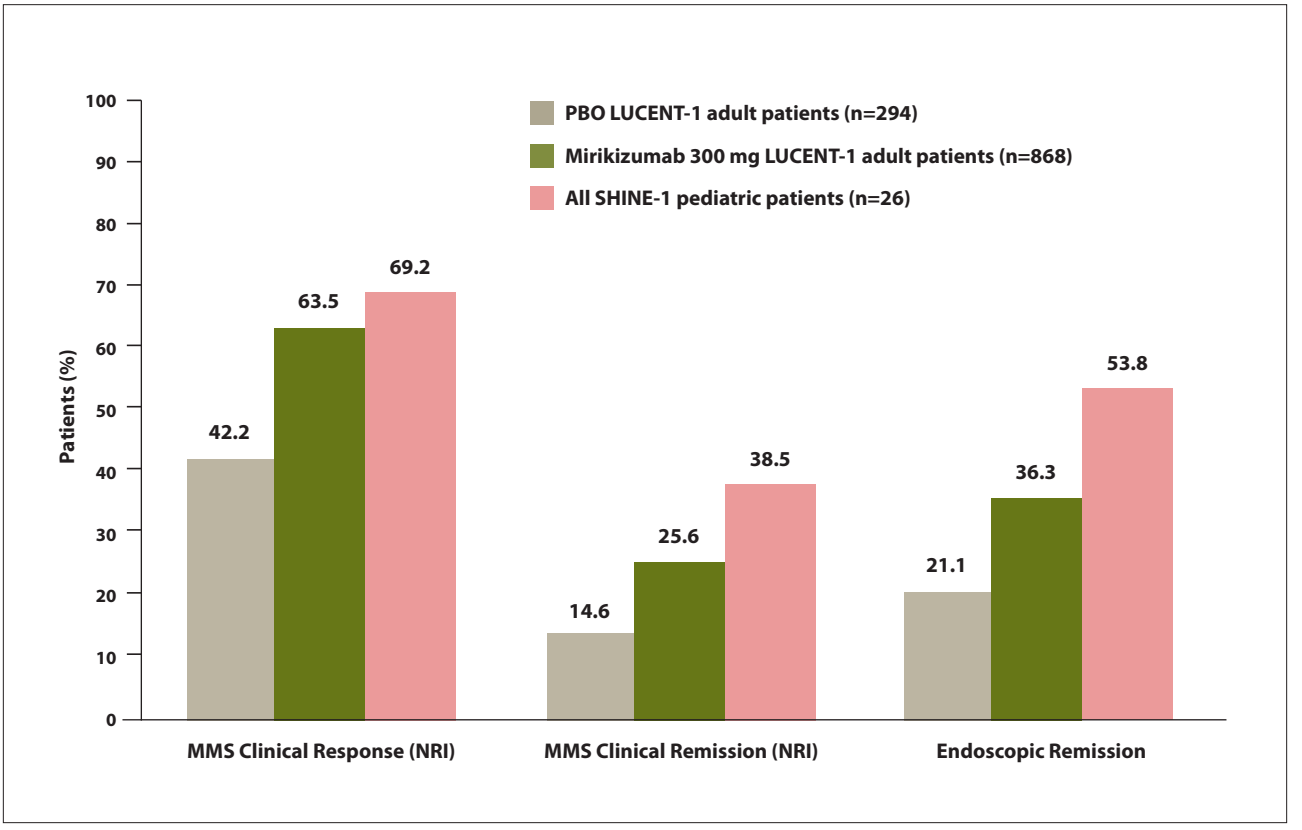

Figure 5. Week 12 MMS clinical response, clinical remission, and endoscopic remission rates for patients treated with mirikizumab from the LUCENT-1 and SHINE-1 trials. MMS, modified Mayo score; NRI, nonresponder imputation; PBO, placebo. Adapted from Kaplan et al. Abstract 781. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[2]

population and define the appropriate doses for the phase 3 study in the same patient setting.

Mirikizumab was administered every 4 weeks to 10 patients who weighed 40 kg or less at a dose of 5 mg/kg and to 5 patients who weighed 40 kg or less at a dose of 10 mg/kg. Mirikizumab at a dose of 300 mg was administered to 11 patients who weighed more than 40 kg. The overall study population of 26 patients had a mean age of 11.8 ± 3.4 years, and 42.3% were male. On the basis of both actual measurements and pharmacokinetic modeling, area under the curve, and maximum plasma concentration, exposure in the patients who received mirikizumab (10 mg/kg) was approximately 2-fold higher than the mean values in adults. In the other 2 groups of pediatric patients, the mean exposure to mirikizumab was similar to that observed in adults.

Outcomes in pediatric patients in the SHINE-1 study were comparable with or better than outcomes in adults in the LUCENT-1 trial, including clinical response by modified Mayo score (69.2% vs 63.5%), clinical remission by modified Mayo score (38.5% vs 25.6%), and endoscopic remission (53.8% vs 36.3%; Figure 5).[3] On the basis of PUCAI scores, the clinical response rate was 76.9% and the clinical remission rate was 38.5%. No new safety signals arose when the pediatric population in SHINE-1 was compared with the adult population in LUCENT-1. Most treatment-emergent AEs were mild, and no serious AEs occurred during the 12-week induction period with mirikizumab.

References

1. Sandborn WJ, Ferrante M, Bhandari BR, et al. Efficacy and safety of mirikizumab in a randomized phase 2 study of patients with ulcerative colitis. *Gastroenterology*. 2020;158(3):537-549.e10.
2. Kaplan J, Bousvaros A, Turner D, et al. PK, efficacy and safety of mirikizumab as induction therapy in pediatric patients with moderately to severely active ulcerative colitis: results from the phase 2 shine-1 study. Abstract 781. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
3. D'Haens G, Kobayashi T, Morris N, et al. 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 [ECCO abstract OP26]. *J Crohns Colitis*. 2022;16(suppl 1).

The Efficacy and Safety of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 QUASAR Induction Study

Guselkumab is a fully human monoclonal antibody that binds to IL-23.[1] The antibody is approved for the treatment of plaque psoriasis and psoriatic arthritis and is under investigation in inflammatory bowel disease. The phase 3 QUASAR study investigated the safety and efficacy of guselkumab induction therapy in patients with moderately to severely active UC.[2] The double-blind, parallel-group, multicenter, randomized, placebo-controlled trial enrolled patients who had had an inadequate response to or could not tolerate conventional and/or advanced therapies. Patients were required to have a modified Mayo score of 5 to 9, a rectal bleeding score of 1 or lower, and an endoscopy subscore no higher than 2. Patients were randomized 3:2 to receive intravenous guselkumab (200 mg) or placebo at weeks 0, 4, and 8. The primary endpoint was clinical remission at week 12, defined as a Mayo stool frequency subscore of 0 or 1 with no increase from baseline, a rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability.

The trial randomized 701 patients with a mean age of 40.5 years and a mean duration of UC of 7.5 years. The mean modified Mayo score was 6.9. Severe disease, indicated by a Mayo endoscopy subscore of 3, was observed

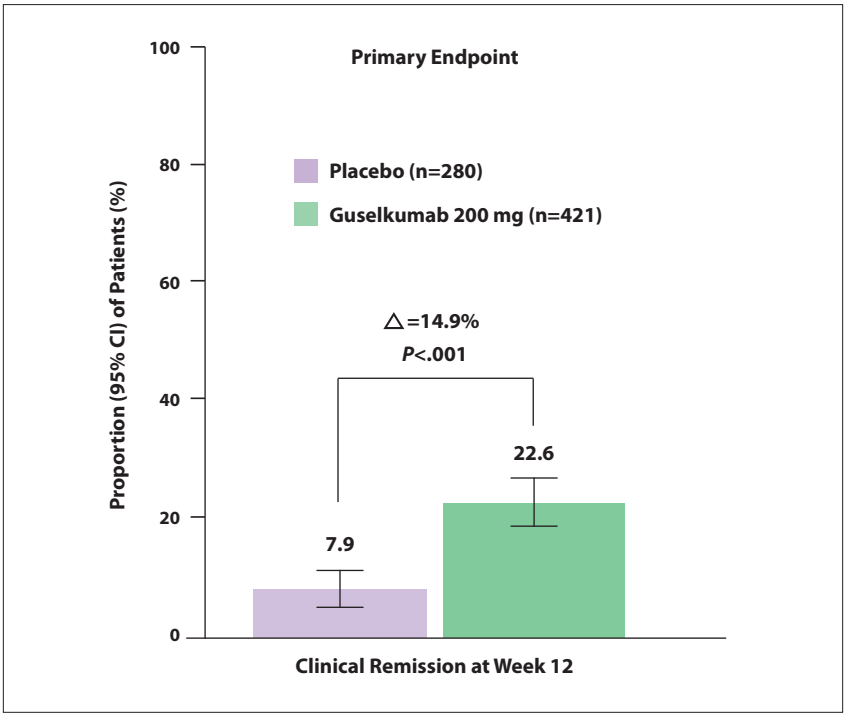

Figure 6. Comparison of the proportions of patients in clinical remission at week 12 treated with guselkumab or placebo. Adapted from Allegretti et al. Abstract 913b. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[2]

in more than two-thirds (67.9%) of the study population. The trial met its primary endpoint, demonstrating clinical remission rates of 22.6% with guselkumab and 7.9% with placebo at week 12 (P<.001; Figure 6). In a comparison of the guselkumab arm and the placebo arm at week 12, the rates of symptomatic remission were 49.9% vs 20.7% (P<.001) and the rates of clinical response were 61.5% vs 27.9% (P<.001), respectively. Also at week 12, the rate of endoscopic improvement with guselkumab was superior to the rate with placebo (26.8% vs 11.1%; P<.001), as was the rate of histologic-endoscopic improvement (23.5% vs 7.5%; P<.001).

Safety data were consistent with the known safety profile of guselkumab observed in patients with the approved indications.[3] In a comparison of the guselkumab and placebo arms, the rates of serious AEs were 2.9% vs 7.1% and the rates of AEs leading to discontinuation of study therapy were 1.7% vs 3.9%, respectively. Approximately 15% to 16% of patients in each arm experienced infection of any grade, with serious infection rates of less than 1% in each arm. AEs within 1 hour of infusion were observed in 1.4% of patients in the guselkumab arm and in 0.4% in the placebo arm, none of which were serious.

References

1. Hanzel J, Hulshoff MS, Grootjans J, D'Haens G. Emerging therapies for ulcerative colitis. *Expert Rev Clin Immunol*. 2022;18(5):513-524.
2. Allegretti JR, Peyrin-Biroulet L, Feagan BG, et al. The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: results from the phase 3 Quasar induction study. Abstract 913b. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
3. First phase 3 TREMFYA® (guselkumab) data in inflammatory bowel disease show positive induction results among patients with moderately to severely active ulcerative colitis [press release]. Spring House, Pennsylvania. Johnson & Johnson. May 9, 2023.

Etrasimod for the Treatment of Ulcerative Colitis: Up to 2.5 Years of Pooled Safety Data From Global Clinical Trials

Etrasimod, an investigational oral modulator of the S1P receptor, is in development for the treatment of moderately to severely active UC. The drug selectively activates S1P receptor subtypes 1, 4, and 5. A retrospective analysis was conducted to provide a comprehensive and up-to-date safety analysis of results from

Table 2. AEs of Special Interest Among Patients in the Placebo and UC Cohorts

AEs of Special Interest	Placebo-Controlled UC cohort		All UC Cohort
	Etrasimod (n=629) Patients, n (%)	Placebo (n=314) Patients, n (%)	Etrasimod (n=956) Patients, n (%)
Any AEs	377 (59.9)	162 (51.6)	649 (67.9)
Serious AEs	29 (4.6)	17 (5.4)	70 (7.3)
Any AE leading to study treatment discontinuation	32 (5.1)	8 (2.5)	65 (6.8)
Death	0	0	1 (0.1)
Infections and infestations • Serious infections • Herpes zoster • Opportunistic infections	122 (19.4) 4 (0.6) 2 (0.3) 2 (0.3)	52 (16.6) 5 (1.6) 2 (0.6) 1 (0.3)	55 (5.8) 15 (1.6) 7 (0.7) 3 (0.3)
All cardiac disorders • Bradycardia • AV block, 1st degree • AV block, 2nd degree (Mobitz type I)	25 (4.0) 11 (1.8) 2 (0.3) 2 (0.3)	4 (1.3) 0 0 0	36 (3.8) 14 (1.5) 4 (0.4) 3 (0.3)
Hypertension	13 (2.1)	3 (1.0)	21 (2.2)
Macular edema	2 (0.3)	1 (0.3)	1 (0.2)
Malignancies	0	0	1 (0.1)
Increased alanine aminotransferase	11 (1.7)	2 (0.6)	27 (2.8)
Decreased γ-glutamyl transferase	13 (2.1)	2 (0.6)	32 (3.3)
Posterior reversible encephalopathy syndrome	0	0	0

AE, adverse event; AV, atrioventricular; UC, ulcerative colitis. Adapted from Vermiere et al. Abstract 948. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[1]

etrasimod clinical trials in patients with moderately to severely active UC and up to 2.5 years of exposure to etrasimod.[1] Patient data were taken from placebo-controlled and OLE studies, including the phase 2 OASIS study (NCT02447302), the phase 3 ELEVATE UC 52 study (NCT03945188), and the phase 3 ELEVATE UC 12 study (NCT03996369). Etrasimod was administered daily at a dose of 1 or 2 mg. The placebo-controlled UC cohort included patients who had received either placebo or etrasimod in one of the placebo-controlled trials. A larger group included all patients in the placebo-controlled studies as well as all patients in the OLE studies who had received at least 1 dose of etrasimod.

The analysis included 956 patients who had received at least one dose of etrasimod, comprising 769.3 patient-years of exposure. In the placebo-controlled UC cohort, 52 patients had received etrasimod at a dose of 1 mg, daily, and 577 had received etrasimod at a dose of 2 mg, daily; the placebo group included 314 patients. In the all UC cohort, 956 patients had received at least one dose of etrasimod at either 1 or 2 mg, daily. The proportions of patients with AEs of any grade were 51.6% in the placebo group, 59.9% in the placebo-controlled etrasimod group, and 67.9% in the all UC etrasimod group; the proportions of patients with serious AEs were 5.4%, 4.6%, and 7.3% in the 3 groups, respectively; and the proportions of patients with any AE leading to discontinuation of study treatment were 2.5%, 5.1%, and 6.8%, respectively. No deaths occurred in the placebo-controlled UC cohort. One patient in the all UC cohort experienced a serious AE of neuroendocrine tumor that resulted in death, but the investigator considered this AE not likely to be related to the study therapy (Table 2).

Across the 3 cohorts, rates of serious infections ranged from 0.6% to 1.6%, and rates of herpes zoster ranged from 0.3% to 0.7%. No bradycardia was observed in any patient in the placebo cohort. Although 11 patients in the placebo-controlled UC cohort who were treated with etrasimod (2 mg, daily) experienced bradycardia, 9 of these events were asymptomatic. Other AEs of special interest were observed at similar rates across the 3 cohorts. In conclusion, the safety profile of etrasimod in patients with UC did not appear to change with a treatment duration of up to 2.5 years.

ABSTRACT SUMMARY Efficacy of Ustekinumab for Ulcerative Colitis Through 4 Years: Final Clinical and Endoscopy Outcomes From the UNIFI Long-Term Extension

In final results from the phase 3 UNIFI long-term extension study, the majority of patients with moderately to severely active UC treated with ustekinumab every 8 or 12 weeks achieved clinical remission (58%), endoscopic improvement (67%), clinical response (80%), and a modified Mayo score response (80%) at 4 years (Abstract Tu1722). Among patients who were in clinical remission at baseline or after 1 year of maintenance therapy with ustekinumab, clinical remission was generally maintained with continued ustekinumab therapy in the long-term extension study. No new safety signals were reported.

Reference

1. Vermiere S, Peyrin-Biroulet L, Panés J. Etrasimod for the treatment of ulcerative colitis: up to 2.5 years of pooled safety data from global clinical trials. Abstract 948. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.

Withdrawal Versus Continuation of Thiopurine in Vedolizumab-Treated Patients With Ulcerative Colitis (VIEWS): A Multi-Centre Randomised Controlled Trial

Thiopurine is commonly used in combination with vedolizumab to treat UC; however, the benefit conferred by thiopurine plus vedolizumab in comparison with vedolizumab monotherapy is not clear.[1,2] The randomized, placebo-controlled, multicenter VIEWS study evaluated the efficacy and safety of vedolizumab plus thiopurine followed by vedolizumab alone in patients with UC in remission.[3] The prospective study enrolled adults who had been on therapy with vedolizumab (300 mg, every 8 weeks) plus thiopurine for at least 6 months, had been in steroid-free clinical remission for at least 6 months, and had a Mayo endoscopic score of 0 or 1 or a fecal calprotectin level of less than 100 μg/g. Patients were randomized 1:2 to continue with the combination therapy or to have the thiopurine withdrawn while they continued vedolizumab monotherapy. The primary endpoint was the vedolizumab trough concentration at week 48.

The study included 20 patients who continued with vedolizumab plus thiopurine (arm A) and 42 from whom thiopurine therapy was withdrawn (arm B). In arm A and arm B, patients had median ages of 46.0 and 41.5 years, 75.0% and 50.0% were male,

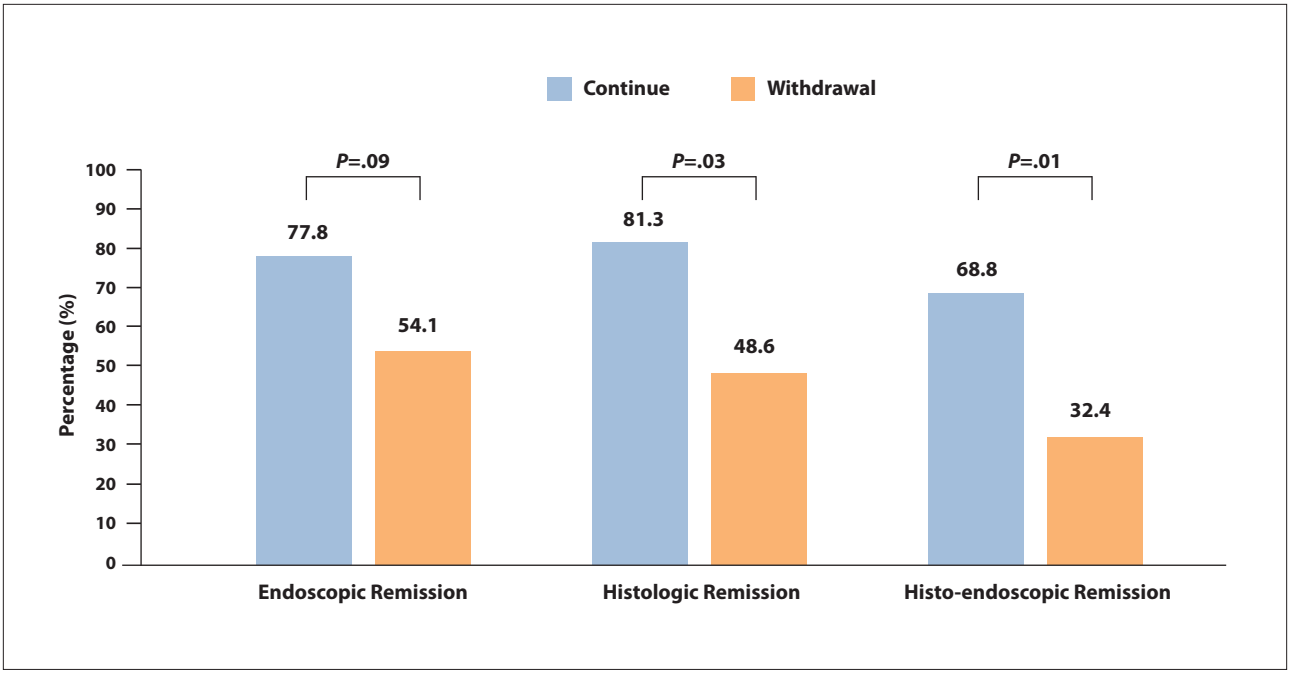

Figure 7. Secondary outcomes of endoscopic remission, histologic remission, and histo-endoscopic remission in thiopurine continue and withdrawal groups. Adapted from Pudipeddi et al. Abstract 1029. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.[3]

and the median disease durations were 6.5 and 8.0 years, respectively. The times on combination therapy before study entry were 47.0 weeks in arm A and 50.0 weeks in arm B. At week 48, the median vedolizumab trough concentrations were not significantly different in the 2 arms (arm A, 14.7% vs arm B, 15.9%; *P*=.36), and the mean changes in the vedolizumab trough concentration from week 0 to week 48 also did not differ significantly between the 2 arms (*P*=.44). The rates of clinical remission were 90% in arm A and 79% in arm B (*P*=.27). Fecal calprotectin remission was observed in 95% vs 71% of patients (*P*=.03) and C-reactive protein remission was documented in 90% vs 67% of patients (*P*=.05) in arm A and arm B, respectively. In arm A and arm B, the rates of endoscopic remission were77.8% and 54.1% (*P*=.09), the rates of histologic remission were 81.3% and 48.6% (*P*=.03), and the rates of histo-endoscopic remission were 68.8% and 32.4% (*P*=.01; Figure 7). On the basis of multivariable analysis, clinical relapse in arm B was predicted by prior anti-TNF exposure (*P*=.009) and histologic activity at baseline (*P*=.002).

ABSTRACT SUMMARY Etrasimod for the Treatment of Ulcerative Colitis: Analysis of Infection Rates From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Clinical Trials

A post hoc study evaluated safety data from 527 patients with moderate-to-severe UC representing 267 patient-years of exposure from the phase 3 ELEVATE UC 52 and ELEVATE UC 52 trials. The analysis showed no increased risk of infection in a comparison of patients with UC treated with etrasimod (EAIR, 0.41) and those treated with placebo (EAIR, 0.52; Abstract Tu1743). EAIRs for serious infections were 0.01 with etrasimod vs 0.05 with placebo, and herpes zoster was less common in patients treated with etrasimod (EAIRs, <.01 and .02). Low absolute lymphocyte counts did not correlate with the development of serious, severe, or opportunistic infection.

References

1. Kirchgesner J, Desai RJ, Schneeweiss MC, Beaugerie L, Schneeweiss S, Kim SC. Decreased risk of treatment failure with vedolizumab and thiopurines combined compared with vedolizumab monotherapy in Crohn's disease. *Gut*. 2022;71(9):1781-1789.
2. Yzet C, Diouf M, Singh S, et al. No benefit of concomitant immunomodulator therapy on efficacy of biologics that are not tumor necrosis factor antagonists in patients with inflammatory bowel diseases: a meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(4):668-679.e8.
3. Pudipeddi A, Paramsothy S, Kariyawasam VC, et al. Withdrawal versus continuation of thiopurine in vedolizumab-treated patients with ulcerative colitis (views): a multi-centre randomised controlled trial. Abstract 1029. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.

Highlights in Ulcerative Colitis From Digestive Disease Week 2023: Commentary

Stephen B. Hanauer, MD
Professor of Medicine
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Presentations on ulcerative colitis (UC) at Digestive Disease Week (DDW) 2023 shed light on significant advances in the understanding, prevention, and treatment of this disease. Data were presented for existing and emerging agents, including ozanimod, tofacitinib, ustekinumab, infliximab, mirikizumab, guselkumab, etrasimod, thiopurine, and vedolizumab.

Ozanimod

Sphingosine-1-phosphate (S1P) modulators are a novel approach to the treatment of inflammatory bowel disease (IBD).[1] One of these modulators, ozanimod, was recently approved for the treatment of moderate to severe UC.[2] Initially, gastroenterologists were concerned about several potential risks associated with ozanimod, such as its effect on the atrioventricular node in the heart, causing bradycardia or alterations in heart rhythm.[3] However, during induction and maintenance in the True North open-label extension study, these events were found to be very uncommon.[4] Similarly, macular edema and worsening of sleep apnea were identified as potential risks, but they were not observed to a significant degree in the induction or 1-year maintenance population.

A study conducted by Dr Maria Abreu and colleagues at the University of Miami looked at the long-term extension of ozanimod treatment, spanning 3 years.[5] The study did not identify any new safety signals or worsening of existing ones. This finding provides substantial reassurance regarding the long-term safety profile of ozanimod. Additionally, other abstracts on ozanimod emphasized not only its safety but also its sustained effectiveness, including clinical improvement over the 3-year period of the open-label extension.[6-8]

Dr Abreu also presented a poster demonstrating the persistence of endoscopic improvement, histologic remission, and mucosal healing, the latter of which is a combination of endoscopic improvement and histologic improvement.[9] It is interesting to note that 97% of the patients continued treatment in the open-label extension for up to 6 months, and this persistence rate remained at about 87% at the end of the year and at 72% after nearly 3 years of treatment. These data provide further reassurance regarding the safety and efficacy of ozanimod. A subsequent abstract from the University of Chicago, which examined the use of ozanimod at the University of Chicago Medical Center, aimed to correlate clinical response with absolute lymphocyte count. Ozanimod works by trapping lymphocytes in the lymph nodes, and treatment with this drug is expected to lead to an approximately 50% reduction in lymphocyte counts.[10] Interestingly, in another abstract, presented at ACG 2022, ozanimod did not cause any increased risk of infection with lymphocyte counts as low as 50% below normal.[11] Unsurprisingly, in the University of Chicago experience, it was observed that efficacy was greater in patients who had a 75% reduction in their absolute lymphocyte count.[10] Other S1P modulators that are currently in development may have greater potency in lowering lymphocyte counts by trapping lymphocytes in the lymph nodes. Further research is needed to determine their effectiveness in comparison with ozanimod.

Tofacitinib vs Ustekinumab

The TORUS study, presented by Dr Anthony Buisson, from France, aimed to compare the effectiveness of tofacitinib, an oral Janus kinase (JAK) inhibitor, with that of ustekinumab in patients with UC who had previously been exposed to at least one anti–tumor necrosis factor (anti-TNF) agent.[12] With various advanced agents, including ustekinumab, risankizumab, vedolizumab, tofacitinib, upadacitinib, and S1P modulators, an increased absolute response rate has been observed in bio-naïve populations. Several attempts have been made to conduct network meta-analyses specifically in patients with prior exposure to biologics, which are almost always TNF blockers.

In this multicenter, retrospective study, the researchers reviewed outcomes with either tofacitinib or ustekinumab in a series of patients who had prior inadequate responses to TNF blockers. The study included nearly 300 patients; 124 received tofacitinib and 165 received ustekinumab. The patients were all comparable in terms of demographic features, age, disease distribution, and severity. Additionally, the 2 groups were matched with propensity scores, ensuring that most

of the patients were being compared with other patients similar in age and general demographics. The study examined several different endpoints, including corticosteroid-free remission at 4 months after the initiation of therapy. The rates of remission were comparable; approximately 38% of those in the tofacitinib group and 36% in the ustekinumab group achieved this important endpoint. Results for subsequent endpoints continued to be similar in the tofacitinib and ustekinumab groups as the patients were followed over time. It is important to note that this study is retrospective and therefore subject to potential bias.

Although head-to-head trials would be desirable, it is unfortunate that as the number of advanced therapies for IBD, UC, and Crohn's disease continues to grow, conducting such trials becomes a challenge. Therefore, it is crucial to accumulate more real-world evidence to compare and eventually prioritize these treatments. Of note, patients with prior biologic exposure in UC demonstrated comparable responses. This means that patients have the option to choose among an oral agent, a JAK inhibitor such as tofacitinib, and a parenteral subcutaneous formulation such as ustekinumab.

Infliximab

Regarding the treatment of UC with intravenous biologic agents like infliximab, several important observations have been made. Traditionally, therapeutic drug monitoring has focused on reactive measures—specifically, trough levels of biologic agents taken right before a scheduled intravenous or subcutaneous administration. These measurements have been helpful to determine how to approach patients with an initial response that was later lost. For patients with low drug levels, treatments are often escalated to higher doses or shorter intervals, and those with antidrug antibodies are switched to another therapy within the same class. Patients who have good drug levels at trough but whose condition does not improve may be switched to a drug with a different mechanism of action.

In the past 5 to 10 years, proactive therapeutic drug monitoring has been the subject of much debate. Although 2 trials from Europe, TAXIS and TAILORx, failed to demonstrate benefits, an underlying theme is that we can improve treatment outcomes, as in many cases responses are lost or inadequate because of initial dosing.[13,14] This problem has been particularly evident in patients with severe UC; researchers in Amsterdam measured infliximab levels in their stool samples. These measurements indicated increased clearance, which refers to the rate at which a drug is eliminated from the body. Consequently, we are learning that several factors contribute to faster clearance, and that more intensive dosing or shorter intervals are necessary for patients with rapid clearing from the start.

In their study, Rosen and colleagues, from Stanford University, evaluated infliximab clearance in relation to disease activity during induction and maintenance therapy in a pediatric population with acute severe UC, both in the hospital and in the ambulatory setting.[15] The study demonstrated that in comparison with adults, pediatric patients with severe UC have higher clearance rates, which correlate with increased severity of clinical disease; this finding supports the need for higher dosing. In our hospitalized patients with severe UC, we adjust dosing on the basis of clearance, using albumin as a clearance marker. Patients with low albumin levels have a high clearance rate and are initially dosed with 10 mg/kg. Then, we monitor the C-reactive protein (CRP) level. If it drops as expected and then starts to rise, we initiate re-treatment within days of the initial dose.

A practical challenge is measuring clearance accurately and adjusting dosing more rapidly. Currently, because of the relatively slow turnover in drug levels (which may take 5-7 days), estimating clearance may be necessary. It has been proved that albumin is the best marker for increased clearance in these patients.

Mirikizumab

Mirikizumab is a monoclonal antibody that targets the p19 subunit of interleukin-23 (IL-23). It is currently being investigated and approaching approval for the treatment of moderate to severe UC in adults.[16] It is also likely to be evaluated and found effective in moderate to severe Crohn's disease,

ABSTRACT SUMMARY Efficacy and Safety Outcomes in Patients With Moderate to Severe Ulcerative Colitis Stratified by Ethnicity and Race: A Pooled Analysis of Data From GEMINI 1, VARSITY, and VISIBLE 1

The phase 3/3b GEMINI, VARSITY, and VISIBLE 1 trials investigated vedolizumab vs adalimumab or placebo in patients with moderately to severely active UC (Abstract 1741). A post hoc study suggested that outcomes in non-White patients were worse than outcomes in patients of White ethnicity. However, robust conclusions could not be drawn because of the small proportion of patients representing minority ethnic groups (10.9% Asian, 1.0% Black, and 1.8% Other). Clinical trials could be improved by recruiting a diverse population that represents patients treated in a real-world setting.

as we have seen positive results from treatment with other agents that target IL-23, such as ustekinumab and risankizumab.[17,18]

Kaplan and colleagues conducted the SHINE study, which evaluated the pharmacokinetics, efficacy, and safety of mirikizumab as induction therapy in pediatric patients with moderately to severely active UC.[19] Similar to what we saw in adult patients with UC, mirikizumab demonstrated pharmacokinetics similar to those reported in the LUCENT study, as well as similar initial efficacy and safety.[20]

Over the past several years, it has been recognized that this class of IL-23 blockers, including p40 in the setting of ustekinumab and the p19 subunit with risankizumab, mirikizumab, and guselkumab, show great efficacy and remarkable safety in Crohn's disease and UC.[21] IL-23 is a prominent cytokine in the skin of patients with psoriasis and in the indices of patients with psoriatic arthritis. However, unlike blocking TNF, targeting IL-23 does not have the same systemic effect on infection risk. IL-23 inhibition is becoming an acceptable and promising approach in terms of both efficacy and safety for the treatment of Crohn's disease.

Guselkumab

Like mirikizumab, guselkumab is an anti–IL-23 antibody that targets the p19 subunit. It is currently being evaluated in both Crohn's disease and UC. Jessica Allegretti, from the Brigham and Women's Hospital, and colleagues presented results from the QUASAR phase 3 study.[22] This randomized, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of guselkumab in adults with moderate to severe UC. As anticipated, given the positive outcomes observed with other therapies targeting IL-23 in UC and Crohn's disease, the researchers found that 3 intravenous 200-mg doses of guselkumab, given 1 month apart, were both safe and effective in treating patients with moderate to severe UC.

Etrasimod

Etrasimod is an oral S1P modulator that is currently being evaluated in moderate to severe UC.[23] Initial results of its efficacy were presented at the European Crohn's and Colitis Organisation (ECCO) Congress and the United European Gastroenterology Week. Severine Vermiere, from Leuven, Belgium, and colleagues also looked at its safety in 2.5 years of global clinical trials in UC.[24] Like ozanimod, etrasimod demonstrated persistent safety, with no new safety signals identified during the 2.5 years following the initial induction studies. The most common side effects were serious infections, including herpes zoster. Surprisingly, these infections were more common in placebo-treated patients. It is worth noting that in other settings, S1P and other advanced agents have been associated with a slightly increased risk of herpes zoster. As a result, it has become routine practice to recommend age-appropriate vaccines, including pneumococcal and shingles vaccines, as soon as possible before therapy with advanced agents is initiated to mitigate the increased risk. It is interesting to note that etrasimod was not associated with an elevated risk of herpes zoster during the extension phase.

Thiopurine and Vedolizumab

Historically, when newer biologic agents like vedolizumab, ustekinumab, risankizumab, and guselkumab are evaluated, patients participating in clinical trials may or may not have been on immunomodulators. None of these studies have been able to demonstrate that concomitant therapy with an immunomodulator is superior. This lack of benefit from combining immunomodulators with biologics was first shown in the ACCENT study of infliximab in Crohn's disease 20 years ago.[25] These studies, including current ones, were not designed with sufficient statistical power to establish a difference between the outcomes of patients on immunomodulators and those of patients not on immunomodulators. Also, patients were not randomized according to their use of immunomodulators. The subsequent SONIC study, which prospectively randomized patients to infliximab alone, azathioprine alone, or combination therapy, found that the combination was better.[26] However, similar investigations have not yet been conducted with other biologic therapies.

In a trial by Pudipeddi and colleagues, the focus was on evaluating the potential risks and benefits of withdrawing immunomodulator therapy from patients who were already receiving it.[27] This trial aimed to determine whether discontinuing immunomodulator therapy would have any significant benefit. Previous studies, such as the STORI study with infliximab, have shown that patients who were on combination therapy and from whom azathioprine was withdrawn could continue to do well if they were in clinical, endoscopic, and histologic remission.[28] Therefore, in the retrospective study by Pudipeddi and colleagues, it was observed that when azathioprine was withdrawn from patients who were not in a state of clinical, endoscopic, and histologic remission, they did not do as well as patients who had continued the combination therapy.[27]

I believe this finding is consistent with the messaging we have regarding individuals who request to withdraw from combination therapy. We have found that withdrawing the immunomodulator is generally acceptable if the patients are in a clinical, endoscopic, and as deep a remission as possible, whether in the context of UC or Crohn's disease. It is also reassuring to assess the drug level of the biologic and ensure that it is adequate at the time of the assessment. For instance, if no drug level is detectable, I would discontinue the biologic and continue with the immunomodulator. In summary, although both the immunomodulator or the other agent can be withdrawn, it is generally considered safer to withdraw the immunomodulator than the

biologic, especially if the patients are in deep remission.

Disclosure

Dr Hanauer has served as a consultant for AbbVie, Allergan, Amgen, Arena, BMS, Boehringer Ingelheim, Celgene, Celltrion Healthcare, Fresenius Kabi, Genentech, Gilead, GSK, Intercept Pharmaceuticals, Janssen, Lilly, Merck, Morphic Therapeutic, Novartis, Pfizer, Progenity, Prometheus, Protagonist, Receptos, Salix Pharmaceuticals, Samsung Bioepis, Seres Therapeutics, Takeda, and TTL Pharma; has received clinical research support to his institution from AbbVie, Amgen, Celgene, Genentech, Gilead, GSK, Janssen, Lilly, Novartis, Pfizer, Prometheus, Receptos, Seres Therapeutics, Takeda, and TLL Pharma; and is a member of the Data and Safety Monitoring Board (DSMB) or data monitoring committee of Allergan, Arena, Boehringer Ingelheim, BMS, Gossamer, Protagonist, and Ventyx.

References

1. Choden T, Cohen NA, Rubin DT. Sphingosine-1 phosphate receptor modulators: the next wave of oral therapies in inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2022;18(5):265-271.
2. U.S. Food and Drug Administration approves Bristol Myers Squibb's Zeposia® (ozanimod), an oral treatment for adults with moderately to severely active ulcerative colitis [press release]. New York, New York. Bristol Myers Squibb. May 27, 2021.
3. Zhao Z, Lv Y, Gu Z-C, Ma CL, Zhong MK. Risk for cardiovascular adverse events associated with sphingosine-1-phosphate receptor modulators in patients with multiple sclerosis: insights from a pooled analysis of 15 randomised controlled trials [published online December 7, 2021]. *Front Immunol.* doi:10.3389/fimmu.2021.795574.
4. Sandborn WJ, Feagan BG, D'Haens G, et al; True North Study Group. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2021;385(14):1280-1291.
5. Abreu M, Danese S, Wolf D, et al. Long-term safety of 3 years of ozanimod in moderately to severely active ulcerative colitis: an interim analysis of the true north open-label extension. Abstract 950. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
6. Cohen NA, Choi D, Garcia NM, et al. Real-world effectiveness and safety of ozanimod: one-year follow-up from a large tertiary center. Abstract Tu1803. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
7. Chiorean M, Colombel J-F, Rubin DT, et al. Achievement and maintenance of endoscopic, histologic, and combined outcomes after extended induction in week 10 nonresponders of ozanimod: 2-year interim analysis of the true north open-label extension study. Abstract Tu1745. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
8. Regueiro M, Dignass A, Colombel J-F, et al. Endoscopic, histologic, and combined outcomes with reinitiation of ozanimod after temporary discontinuation: 2-year interim analysis of the true north open-label extension study. Abstract Tu1742. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
9. Abreu MT, Danese S, Wolf DC, et al. Effects of ozanimod on histologic remission and mucosal healing over 3 years of continuous treatment in patients with ulcerative colitis. Abstract Tu1725. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
10. Rubin DT, Colombel JF, Chiorean MV, et al. Extended induction in the true north open-label extension study: clinical outcomes of ~2 years of ozanimod treatment. Abstract Tu1736. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
11. Harris S. Association between absolute lymphocyte count and ozanimod efficacy/safety in patients with moderate/severe ulcerative colitis: results from the phase 3 True North study. Abstract E0354. ACG 2022; October 21-26, 2022; Charlotte, North Carolina.
12. Buisson A, Serrero M, Altwegg R, et al. Real-world comparison of effectiveness between tofacitinib and ustekinumab in patients with UC exposed to at least one anti-TNF agent: result from the TORUS study. Abstract 14. Presented at: DDW 2023; May 7-9, 2023; Chicago, Illinois.
13. ClinicalTrials.gov. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS) (TAXIS). Updated December 22, 2022. Accessed June 6, 2023.
14. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379(2):111-121.
15. Rosen MJ, Rabizadeh S, Panetta JC, et al. Infliximab clearance in relation to disease activity during induction and maintenance therapy of acute severe and ambulatory pediatric ulcerative colitis. Abstract 714. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
16. Lilly discloses first-in-class, interim phase 2 data in pediatric patients and new analysis from phase 3 program in adult patients for mirikizumab in ulcerative colitis [press release]. Indianapolis, Indiana. Lilly; May 9, 2023.
17. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2016;375(20):1946-1960.
18. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet.* 2022:399(10340):2015-2030.
19. Kaplan J, Bousvaros A, Turner D, et al. PK, efficacy and safety of mirikizumab as induction therapy in pediatric patients with moderately to severely active ulcerative colitis: results from the phase 2 SHINE-1 study. Abstract 781. Presented at: DDW 2023; May 7-9, 2023; Chicago, Illinois.
20. 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. *Gastroenterol Hepatol (N Y).* 2022;18(4)(suppl 1):7-8.
21. Parigi TL, Iacucci M, Ghosh S. Blockade of IL-23: what is in the pipeline? *J Crohns Colitis.* 2022;16(2)(suppl 2):ii64-ii72.
22. Allegretti JR, Peyrin-Biroulet L, Geagan BG, et al. The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: results from the phase 3 quasar induction study. Abstract 913b. Presented at: DDW 2023; May 76-9, 2023; Chicago, Illinois.
23. Wils P, Peyrin-Biroulet L. Etrasimod for the treatment of ulcerative colitis. *Immunotherapy.* 2023;15(5):311-321.
24. Vermiere S, Peyrin-Biroulet L, Panes J, et al. Etrasimod for the treatment of ulcerative colitis: up to 2.5 years of pooled safety data from global clinical trials. Abstract 948. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
25. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet.* 2002;359(9317):1541-1549.
26. Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010;362(15):1383-1395.
27. Pudipeddi A, Paramsothy S, Kariyawasam VC, et al. Withdrawal versus continuation of thiopurine in vedolizumab-treated patients with ulcerative colitis (views): a multi-centre randomised controlled trial. Abstract 1029. Presented at: DDW 2023; May 6-9, 2023; Chicago, Illinois.
28. Reenaers C, Mary J-Y, Nachury M, et al; Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif. Outcomes 7 years after infliximab withdrawal for patients with Crohn's disease in sustained remission. *Clin Gastroenterol Hepatol.* 2018;16(2):234-243.e2.

ABSTRACT SUMMARY Safety of Upadacitinib in Ulcerative Colitis: Long-Term Data From the Phase 3 Open-Label Extension Study (U-ACTIVATE)

In the open-label extension study of the phase 3 U-ACTIVATE trial, long-term safety with upadacitinib (15 or 30 mg, daily) was similar to that in prior data from the 52-week U-ACHIEVE maintenance study in patients with moderately to severely active UC (Abstract Tu1732). In 1308 patients representing 2350 patient-years of exposure to upadacitinib, rates of treatment-emergent AEs, AEs of special interest, and malignancies were consistent with prior safety results in patients with UC.

Notes


G&H