

A SPECIAL MEETING REVIEW EDITION

Highlights in Inflammatory Bowel Disease From the 14th Congress of ECCO

A Review of Selected Presentations From the 14th Congress of the European Crohn's and Colitis Organisation (ECCO) • March 6-9, 2019 • Copenhagen, Denmark

Special Reporting on:

- VARSITY: A Double-Blind, Double-Dummy, Randomized Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis
- Analyses of Data From the VISIBLE 1 and 2 Trials: Vedolizumab in Patients With Ulcerative Colitis or Crohn's Disease
- Improved Endoscopic Outcomes and Mucosal Healing of Upadacitinib as an Induction Therapy in Adults With Moderately to Severely Active Ulcerative Colitis: Data From the U-ACHIEVE Study
- Long-Term Safety of Vedolizumab in Ulcerative Colitis and Crohn's Disease: Final Results From the GEMINI LTS Study
- Pediatric Crohn's Disease Adalimumab Level-Based Optimization Treatment (PAILOT) Randomized Controlled Trial
- Maintenance Treatment With Mirikizumab, a P19-Directed IL-23 Antibody: 52-Week Results in Patients With Moderately to Severely Active Ulcerative Colitis
- Real-World Effectiveness and Safety of Vedolizumab and Anti-TNF Therapy in Biologic-Naive Patients With Ulcerative Colitis or Crohn's Disease: Results From the EVOLVE Study
- A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of a Targeted-Release Oral Cyclosporine Formulation in the Treatment of Mild to Moderate Ulcerative Colitis: Efficacy Results
- Real-World Analyses of Patients With IBD Treated With Vedolizumab

PLUS Meeting Abstract Summaries

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It Began

In UC & Crohn's

FOR ADULTS WITH MODERATELY TO SEVERELY ACTIVE UC OR CD FOR WHOM OTHER THERAPIES HAVE NOT WORKED WELL ENOUGH

Your decision to prescribe Entyvio for your appropriate patients may change the next chapter of their treatment journey

Only Entyvio combines:

LONG-TERM REMISSION — **AND** —

UC and CD patients achieved remission at 52 weeks vs placebo in study populations that included bio-naïve and anti-TNF α -experienced patients^{1,2}

Individual results may vary.

INDICATIONS

Adult Ulcerative Colitis (UC)

ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission.

Adult Crohn's Disease (CD)

ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission.

IMPORTANT SAFETY INFORMATION

- ENTYVIO (vedolizumab) for injection is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.
- Infusion-related reactions and hypersensitivity reactions including anaphylaxis have occurred. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.
- Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.

With... Entyvio[®] vedolizumab

GUT SELECTIVITY³⁻⁸

Entyvio helps address inflammation where it occurs—in the gut

Entyvio specifically binds to the $\alpha 4\beta 7$ integrin and blocks the interaction between the $\alpha 4\beta 7$ integrin and MAdCAM-1, which is mainly expressed on GI tract endothelial cells¹

AND

SAFETY FOR THE LONG TERM

Clinical trials evaluated in more than 3300 patients; the 5-year analysis that included an open-label continuation study demonstrated consistent results across safety parameters^{1,9}

IMPORTANT SAFETY INFORMATION (continued)

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.
- Most common adverse reactions (incidence $\geq 3\%$ and $\geq 1\%$ higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see brief summary of Prescribing Information on adjacent pages.

MAdCAM-1 = mucosal addressin cell adhesion molecule-1.

References: **1.** Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **2.** Data on file. Takeda Pharmaceuticals America, Inc. Deerfield, IL. **3.** Briskin M, Winsor-Hines D, Shyjan A, et al. *Am J Pathol.* 1997;151(1):97-110. **4.** Fedyk E, Wyant T, Yang LL, et al. *Inflamm Bowel Dis.* 2012;18(11):2107-2119. **5.** Soler D, Chapman T, Yang LL, et al. *J Pharmacol Exp Ther.* 2009;330(3):864-875. **6.** Wyant T, Fedyk E, Abhyankar B. *J Crohns Colitis.* 2016;10(12):1437-1444. **7.** Wyant T, Leach T, Sankoh S, et al. *Gut.* 2015;64(1):77-83. **8.** Milch C, Wyant T, Xu J, et al. *J Neuroimmunol.* 2013;264:123-126. **9.** Colombel JF, Sands BE, Rutgeerts P, et al. *Gut.* 2017;66(5):839-851.

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Learn how you can help your patients reach remission—visit EntyvioHCP.com



BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ENTYVIO (vedolizumab) for injection, for intravenous use

INDICATIONS AND USAGE

Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate) [see *Warnings and Precautions and Adverse Reactions*].

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) [see *Adverse Reactions*]. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYVIO may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment (e.g., epinephrine and antihistamines).

Infections

Patients treated with ENTYVIO are at increased risk for developing infections [see *Adverse Reactions*]. The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, *Listeria meningitis*, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML), see *Warnings and Precautions*.

Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are

diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury [see *Adverse Reactions*].

Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO [see *Adverse Reactions*].

ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions [see *Warnings and Precautions*]
- Infections [see *Warnings and Precautions*]
- Progressive Multifocal Leukoencephalopathy [see *Warnings and Precautions*]
- Liver Injury [see *Warnings and Precautions*]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 835 exposed for greater than two years.

The safety data described in *Table 2* are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

In these trials, 1,434 patients received ENTYVIO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn's disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9%, with placebo).

The most common adverse reactions (reported by $\geq 3\%$ of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and $\geq 1\%$ higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (*Table 2*).

Table 2. Adverse Reactions in $\geq 3\%$ of ENTYVIO-treated Patients and $\geq 1\%$ Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO [†] (N=1434)	Placebo [‡] (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

[†]Patients who received ENTYVIO for up to 52 weeks.

[‡]Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in Table 2.

Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following ENTYVIO administration in clinical trials [see *Warnings and Precautions*]. In UC Trials I and II and Crohn's Trials I and III, one case of anaphylaxis [one out of 1434 patients treated with ENTYVIO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with ENTYVIO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with ENTYVIO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with ENTYVIO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with ENTYVIO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to pretreat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with ENTYVIO and 0.7 per patient-year in the patients treated with placebo [see *Warnings and Precautions*]. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with ENTYVIO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with ENTYVIO, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, *Listeria meningitis*, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with ENTYVIO died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving ENTYVIO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO [see *Warnings and Precautions*]. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations $\geq 3 \times$ ULN was <2% in patients treated with ENTYVIO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to vedolizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In UC Trials I and II and CD Trials I and III, in patients who received ENTYVIO, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVIO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects

with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

DRUG INTERACTIONS

Natalizumab

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

Live Vaccines

Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks [see *Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

Pregnancy Category B:

Risk Summary

There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

Clinical Considerations

Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Manufactured by:

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

U.S. License No. 1898

For more information, go to www.ENTYVIO.com or call 1-877-825-3327

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VARSITY: A Double-Blind, Double-Dummy, Randomized Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis

In the late-breaking abstract session, Dr Stefan Schreiber and colleagues presented results of the phase 3b VARSITY study (A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis), which compared vedolizumab vs adalimumab for the treatment of ulcerative colitis.¹ Vedolizumab is a gut-selective, humanized immunoglobulin G1 monoclonal antibody directed against the $\alpha 4\beta 7$ integrin. It is administered intravenously (IV). Adalimumab is a subcutaneously (SC)-administered human immunoglobulin G1 monoclonal antibody that binds to and neutralizes the cytokine tumor necrosis factor α (TNF α) with systemic effects. VARSITY is one of the first large clinical trials to conduct a head-to-head comparison of 2 biologic agents in patients with inflammatory bowel disease (IBD). The trial followed a randomized, double-blind, double-dummy, multicenter, active-control phase 3b design to compare the efficacy and safety of vedolizumab vs adalimumab at week 52 in patients with moderately to severely active ulcerative colitis.

After an initial screening period, patients were randomly assigned to 52 weeks of treatment with vedolizumab (300 mg IV at weeks 0, 2, 6, and every 8 weeks thereafter) or adalimumab (160 mg SC at week 0, 80 mg SC at week 2, and 40 mg SC every 2 weeks thereafter).¹ To keep the study double-blind, patients in the vedolizumab arm were additionally treated with a SC placebo, and patients in the adalimumab arm received an IV placebo. Patients were assessed at baseline and at weeks 14 and 52 by endoscopy. After the 52-week study was completed, patients were followed for an additional 18 weeks via clinic visits, and then by telephone for

up to 6 months after completing their last dose.

The primary endpoint of the VARSITY study was the proportion of patients achieving clinical remission at week 52. Clinical remission was defined as a complete Mayo score of 2 or lower and no individual subscore higher than 1. Secondary endpoints included the proportion of patients achieving mucosal healing (Mayo endoscopic subscore, ≤ 1) at week 52 and the proportion of patients who discontinued oral corticosteroids and were in clinical remission at week 52.

The study randomly assigned 771 patients with ulcerative colitis to treatment with vedolizumab or adalimumab in a 1:1 fashion. The baseline characteristics were balanced between the 2 treatment arms. The mean age was 40.8 years in the vedolizumab arm and 40.5 years in the adalimumab arm; 60.8% and 56.0% of patients in each arm, respectively, were male. At baseline, the rates of severe ulcerative

colitis (Mayo score 9-12) were 56.4% in the vedolizumab arm and 54.4% in the adalimumab arm. Moderate disease (Mayo score 6-8) was reported in 40.0% of the vedolizumab arm and 43.8% of the adalimumab arm. Mild disease (Mayo score < 6) was reported in 2.3% vs 1.3%, respectively. The mean duration of ulcerative colitis disease was 7.25 years in the vedolizumab arm and 6.35 years in the adalimumab arm. Previous treatment with anti-TNF therapy was reported by 20.8% vs 21.0%. Concomitant corticosteroids were used by 36.1% vs 36.3% of patients, respectively, and concomitant immunomodulators were used by 26.2% vs 25.9%. A total of 74.5% of patients in the vedolizumab arm completed treatment as planned, compared with 61.9% of patients in the adalimumab arm.

In the primary analysis of the overall intention-to-treat population, the primary endpoint of clinical remission at week 52 was reached by 31.3% of the vedolizumab arm vs 22.5% of

ABSTRACT SUMMARY The Impact of Early Disease Control With Vedolizumab on Surgery Rates Among Patients With Crohn's Disease: a Post Hoc Analysis of the GEMINI Trials

A post hoc analysis of the GEMINI 2 and GEMINI long-term safety (LTS) trials evaluated whether early disease control with vedolizumab impacts rates of Crohn's disease-related surgery (defined as any bowel resection; Abstract P537). A clinical decision support tool was used to stratify 1253 patients according to their baseline probability of clinical response to vedolizumab (low: n=356; intermediate: n=631; or high: n=266). Overall, the results of this analysis suggested that vedolizumab treatment earlier in the course of the disease was associated with lower rates of Crohn's disease-related surgery, regardless of baseline probability of clinical response to vedolizumab. The magnitude of the benefit associated with earlier vs later disease control was greatest among patients with a low or intermediate probability of clinical response to vedolizumab. Among patients with a low or intermediate probability, those with a disease duration of 5 years or less had 39% lower odds of requiring Crohn's disease-related surgery compared with patients who had a disease duration lasting longer than 5 years (odds ratio, 0.61; 95% CI, 0.36-0.99).

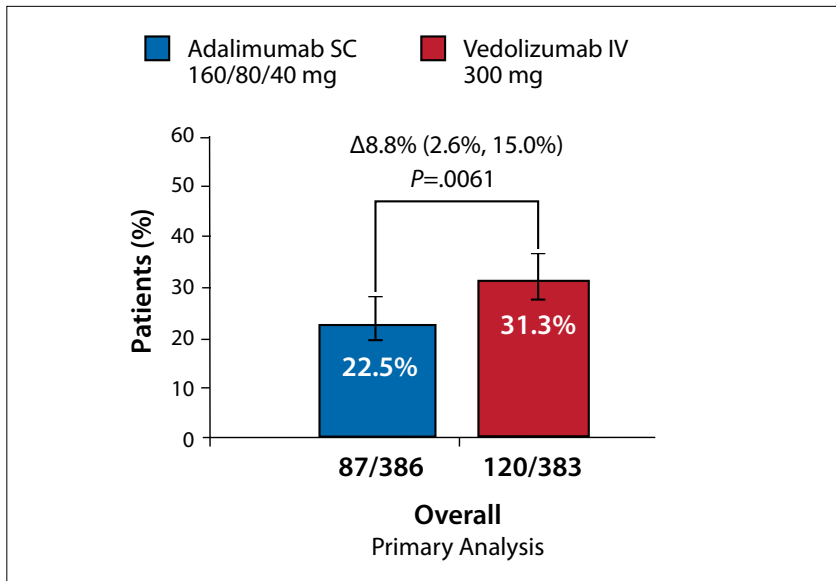


Figure 1. Overall clinical remission at week 52 in the VARSITY trial, which compared vedolizumab vs adalimumab in patients with ulcerative colitis. IV, intravenous; SC, subcutaneous; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Schreiber S et al. ECCO abstract OP34. *J Crohns Colitis*. 2019;13(suppl 1).¹

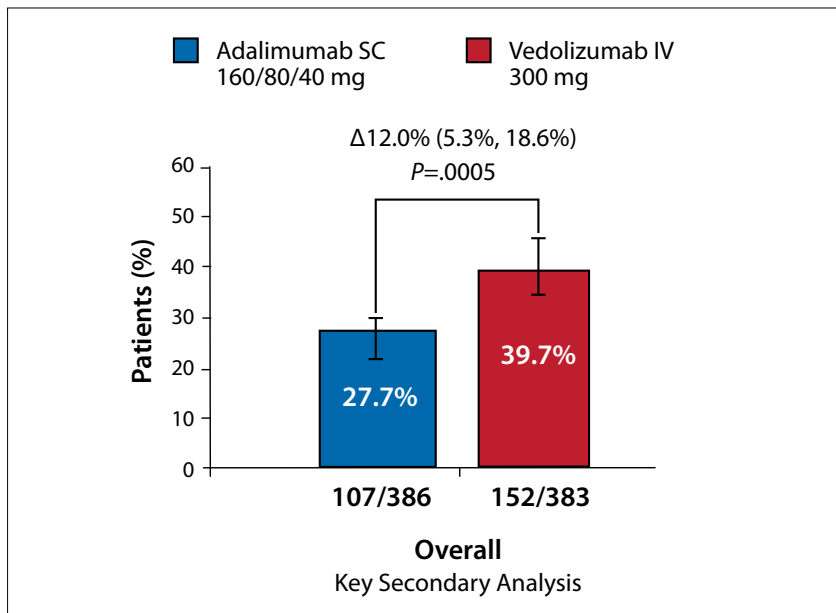


Figure 2. Mucosal healing at week 52 in the VARSITY trial, which compared vedolizumab vs adalimumab in patients with ulcerative colitis. IV, intravenous; SC, subcutaneous; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Schreiber S et al. ECCO abstract OP34. *J Crohns Colitis*. 2019;13(suppl 1).¹

the adalimumab arm (95% CI, 2.6-15.0; $P = .0061$; Figure 1). In a pre-specified subgroup analysis of patients who had not received prior treatment with anti-TNF therapy, the rates of clinical remission at week 52 were 34.2% with vedolizumab vs 24.3% with adalimumab (95% CI, 2.8-17.1; nominal $P = .0070$). Among patients who had received prior anti-TNF agents, clinical remission occurred in 20.3% vs 16.0%, respectively (95% CI, -7.7 to 16.1; nominal $P = .4948$). Assessment of clinical response rates over the 52-week study showed that

treatment differences began to emerge between weeks 6 and 14.

In the overall intention-to-treat population, the secondary endpoint of mucosal healing at week 52 was reported in 39.7% of the vedolizumab arm vs 27.7% of the adalimumab arm (95% CI, 5.3-18.6; $P = .0005$; Figure 2). Among patients who had not received prior treatment with anti-TNF therapy, these rates were 43.1% with vedolizumab vs 29.5% with adalimumab (95% CI, 6.0-21.1; nominal $P = .0005$). The difference in mucosal healing was not statistically

significant among patients who had received prior anti-TNF treatment, at 26.6% with vedolizumab vs 21.0% with adalimumab (95% CI, -7.6 to 18.8; nominal $P = .4136$). The clinical responses according to study visit are shown in Figure 3. The proportion of patients who achieved corticosteroid-free remission at week 52 was 21.7% with adalimumab vs 12.6% with vedolizumab, although this difference did not reach statistical significance. The study investigators noted that the absolute reduction in corticosteroid use was greater with vedolizumab, but

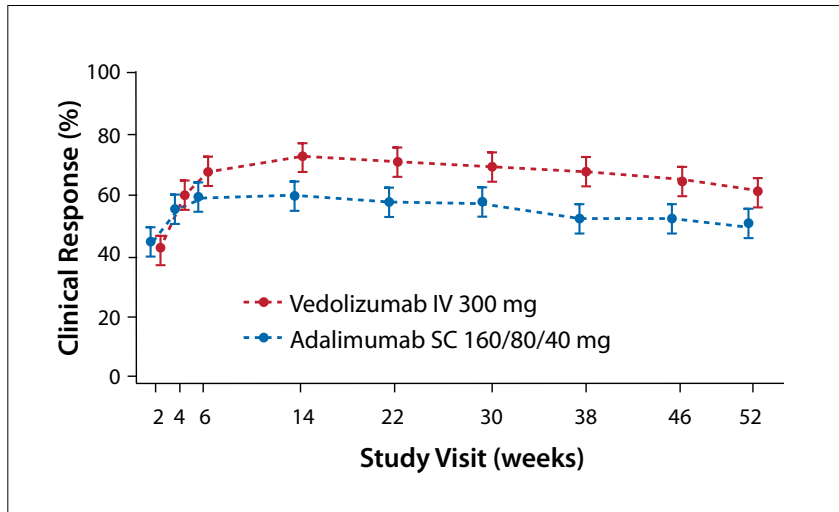


Figure 3. Clinical response by visit based on change in the partial Mayo score from baseline in the VARSITY trial of vedolizumab vs adalimumab in patients with ulcerative colitis. The 95% CI of the percentage, also shown, is based on the Clopper-Pearson method. Clinical response based on the partial Mayo score was defined as a reduction in partial Mayo score of ≥ 2 points and $\geq 25\%$ from baseline, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point. Patients with missing clinical response status were considered nonresponders. The full analysis set included all randomized patients who received ≥ 1 dose of the study drug. IV, intravenous; SC, subcutaneous; VARSITY, A Double-Blind, Double-Dummy, Randomised, Controlled Trial of Vedolizumab Versus Adalimumab in Patients With Active Ulcerative Colitis. Adapted from Schreiber S et al. ECCO abstract OP34. *J Crohns Colitis*. 2019;13(suppl 1).¹

the difference was not significant.

Treatment-related adverse events occurred in 17.0% of the vedolizumab arm vs 22.3% of the adalimumab arm. Serious adverse events related to the study treatment were reported in 1.8% of the vedolizumab arm and 2.6% of the adalimumab arm. Treatment was discontinued owing to an adverse event in 4.4% vs 6.5%, respectively. An analysis of selected exposure-adjusted adverse events showed that an infection or infestation occurred in 33.5% vs 43.5%. Most of these events were upper respiratory tract infections.

The study investigators concluded that the results support the use of vedolizumab before adalimumab in patients with moderately to severely active ulcerative colitis.¹ Both treatments were generally safe and well-tolerated.

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Analyses of Data From the VISIBLE 1 and 2 Trials: Vedolizumab in Patients With Ulcerative Colitis or Crohn's Disease

Several abstracts reported results from the VISIBLE 1 and 2 trials. The VISIBLE 1 trial (Efficacy and Safety of Vedolizumab Subcutaneously [SC] as Maintenance Therapy in Ulcerative Colitis) was a pivotal, multicenter, randomized, double-blind, double-dummy phase 3 study that evaluated vedolizumab SC as maintenance treatment for ulcerative colitis.¹ The rate of clinical remission at week 52 was 46.2% with vedolizumab SC maintenance treatment vs 14.3% with placebo ($P < .001$), a significant difference that met the primary endpoint. VISIBLE 2 (Efficacy and Safety of Vedolizumab Subcutaneous [SC] as Maintenance Therapy in Crohn's Disease) is an ongoing, similarly designed phase 3 trial evaluating vedolizumab SC in patients with Crohn's disease.²

Both studies enrolled patients who had exhibited an inadequate response, loss of response, or intolerance to previous treatment that included corticosteroids, immunosuppressive agents, and/or anti-TNF therapy.

A study evaluated the exposure-response relationship of vedolizumab SC in patients with ulcerative colitis enrolled in the VISIBLE 1 study.³ Vedolizumab trough concentrations were measured at weeks 6 and 46 and grouped into quartiles. The proportion of patients treated with vedolizumab SC for maintenance therapy ($n = 106$) who achieved a clinical remission increased from 50% in quartile 1 to 83% in quartile 4 (Figure 4). Rates of mucosal healing increased from 50% in quartile 1 to 89% in quartile 4. Similar pharmacokinetic trends were observed

among patients randomly assigned to maintenance treatment with vedolizumab IV ($n = 54$). The immunogenicity rate for patients receiving vedolizumab SC was low, at 6%, and similar to that in the vedolizumab IV arm.

Dr Séverine Vermeire and coworkers measured health-related quality of life and work productivity among patients with ulcerative colitis who received vedolizumab in the VISIBLE 1 study.⁴ Mean total IBD questionnaire (IBDQ) scores improved markedly over time in both the vedolizumab SC and IV groups vs placebo. At week 52, clinically meaningful improvements in mean total IBDQ scores were observed with vedolizumab SC (180.7) and vedolizumab IV (170.7), as compared with placebo (135.2). Changes in the total IBDQ score from baseline to

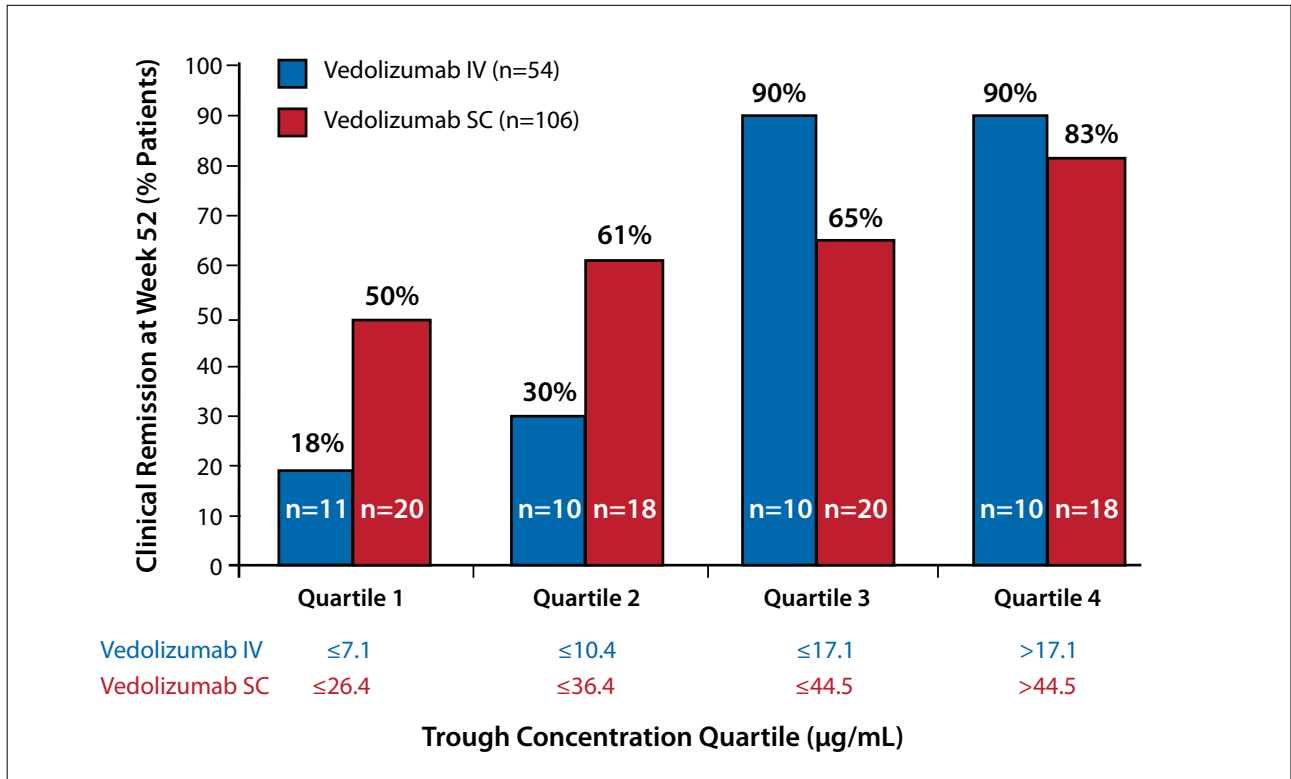


Figure 4. Clinical remission among patients with ulcerative colitis treated with vedolizumab according to trough concentration quartile in the VISIBLE 1 trial. IV, intravenous; SC, subcutaneous; VISIBLE, Efficacy and Safety of Vedolizumab Subcutaneously (SC) as Maintenance Therapy in Ulcerative Colitis. Adapted from Rosario M et al. ECCO abstract P529. *J Crohns Colitis*. 2019;13(suppl 1).³

week 52 were significantly higher for both vedolizumab SC (+65.3) and vedolizumab IV (+58.6) vs placebo ($P < .001$ for both comparisons). In contrast, patients randomly assigned to the placebo arm showed substantial worsening in the IBDQ score through week 52. Similar trends in improvements were observed across the individual IBDQ subscale components, including bowel symptoms, emotional function, social function, and systemic symptoms. Changes in the EuroQoL Quality of Life 5D visual analogue scale score were also significantly greater for vedolizumab SC (+27.1) and vedolizumab IV (+22.6) vs placebo ($P \leq .001$ for both comparisons). Work productivity, as assessed by the Work Productivity and Activity Impairment–Ulcerative Colitis score, also showed improvements with both vedolizumab SC and vedolizumab IV compared with placebo. These

improvements were initially observed at week 6 and sustained through week 52.

Dr Edward V. Loftus Jr and colleagues analyzed data from VISIBLE 1 (patients with ulcerative colitis) and VISIBLE 2 (patients with Crohn's disease) to evaluate the efficacy and safety of 2 vs 3 induction doses of vedolizumab IV.⁵ In both studies, patients received open-label vedolizumab IV induction therapy at weeks 0 and 2. Patients classified as nonresponders at week 6 received a third IV induction infusion at this time, and were reassessed for response at week 14. In contrast, patients with a clinical response at week 6 entered the maintenance phase of the study.

Among the 383 patients with ulcerative colitis, 85.9% had a clinical response after 2 or 3 induction infusions of vedolizumab IV.⁵ In patients with ulcerative colitis, 56.1% had

a clinical response at week 6 after 2 IV infusions. Among the remaining patients with ulcerative colitis, who were classified as nonresponders and received a third induction dose, the rate of clinical response at week 14 was 79.7%. Among the 644 patients with Crohn's disease, 82.6% had a clinical response after either 2 or 3 induction infusions of vedolizumab IV. In patients with Crohn's disease, 63.7% had a clinical response at week 6 after 2 IV infusions. Among the remaining nonresponding patients, who were treated with a third induction dose, the clinical response rate at week 14 was 63.2%. The investigators concluded that patients who do not respond to 2 induction doses with vedolizumab IV appear to benefit from a third induction dose. The safety and tolerability profiles during the induction phase of these studies were consistent with previous reports.

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ABSTRACT SUMMARY Comparative Effectiveness of Vedolizumab and Ustekinumab as Induction Therapy in Anti-TNF Refractory Crohn's Disease: a Multi-Center Retrospective Cohort Study

A multicenter, retrospective cohort study evaluated the efficacy of vedolizumab and ustekinumab for the treatment of Crohn's disease refractory to anti-TNF therapy in a real-world setting (Abstract P586). The analysis included 76 patients from 4 hospitals. Of these, 51 initiated treatment with vedolizumab and 25 with ustekinumab. The patient demographics at baseline were similar between the 2 treatment groups. Patients treated with vedolizumab achieved a significant reduction in the Harvey-Bradshaw Index at 2 months (1.8; 95% CI, 0.50-3.13; $P=.008$). Among patients treated with ustekinumab, a significant reduction in the index was observed at 4 months (3.4; 95% CI, 1.84-4.96; $P=.0001$). The study investigators concluded that vedolizumab and ustekinumab appeared to be equally effective over short-term (up to 4 months) follow-up. At 4 months, vedolizumab and ustekinumab were associated with relatively similar rates of response (49% vs 60%), remission (27% vs 40%), and corticosteroid-free remission (25% vs 36%).

Improved Endoscopic Outcomes and Mucosal Healing of Upadacitinib as an Induction Therapy in Adults With Moderately to Severely Active Ulcerative Colitis: Data From the U-ACHIEVE Study

The double-blind, placebo-controlled phase 2 U-ACHIEVE study was a dose-ranging trial that evaluated upadacitinib, an oral selective Janus kinase 1 inhibitor, in patients with moderately to severely active ulcerative colitis. Patients had exhibited an inadequate response, loss of response, or intolerance to conventional treatment with corticosteroids, biologic agents, or immunosuppressants. The study randomly assigned 250 patients to 5 treatment arms, consisting of 4 different daily doses of upadacitinib (7.5 mg, 15 mg, 30 mg, or 45 mg) or placebo. All patients had ulcerative colitis (confirmed by colonoscopy) diagnosed at least 90 days prior to baseline. Moderately to severely active ulcerative colitis was defined as an adapted Mayo score (which did not include the Physician's Global Assessment) of 5 to 9 points, with an endoscopic subscore of 2 to 3.

Results from the primary analysis of the U-ACHIEVE trial were presented at the 2018 United European Gastroenterology Week.¹ Treatment with upadacitinib (at doses ≥ 30 mg/day) was associated with statistically significant improvements in all primary and ranked secondary endpoints vs placebo. The safety profile and drug discontinuation rates were similar between the treatment arms. Adverse events of special interest were uncommon with upadacitinib (<5%), with the exception of lymphopenia, hepatic disorder, and creatine phosphokinase elevation.

A report from Dr William J. Sandborn and colleagues provided data for endoscopic and histologic outcomes after induction therapy with upadacitinib in the U-ACHIEVE study.² Endoscopic and histologic outcomes were assessed at week 8. Endoscopic improvement was defined as an

endoscopic subscore of 1 or lower, and endoscopic remission was considered an endoscopic subscore of 0. Histologic improvement was defined as any decrease from baseline in the Geboes score, and histologic remission was defined as a Geboes score of less than 2. Mucosal healing was defined as an endoscopic subscore of 0 and a Geboes score of less than 2.

At week 8, rates of endoscopic improvement were significantly higher across all upadacitinib doses vs placebo (Figure 5). Endoscopic improvement was seen in 35.7% of the 45-mg arm vs 2.2% of the placebo arm ($P<.001$). Rates of endoscopic remission were 0% in the placebo arm, vs 9.6% in the 30-mg arm ($P<.05$) and 17.9% in the 45-mg arm ($P<.01$).

Rates of histologic improvement at week 8 were significantly higher across all upadacitinib doses vs placebo. These rates were 51.0% with

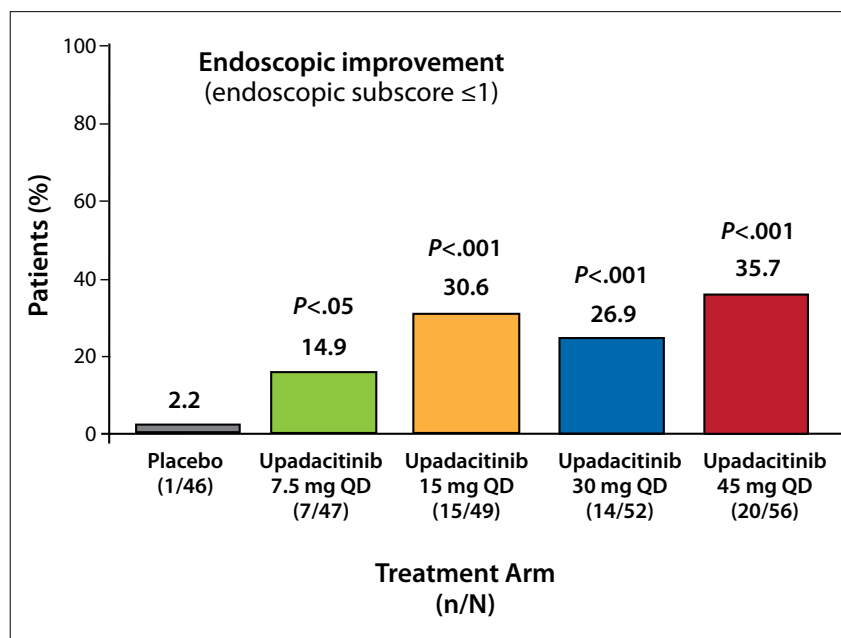


Figure 5. Endoscopic improvement among patients with ulcerative colitis treated with upadacitinib in the U-ACHIEVE study. QD, once daily. Adapted from Sandborn WJ et al. ECCO abstract OP14. *J Crohns Colitis*. 2019;13(suppl 1).²

15 mg, 44.2% with 30 mg, and 48.2% with 45 mg, vs 6.5% with placebo ($P < .001$). Histologic remission rates

were 2.2% with placebo, vs 30.8% in the 30-mg arm ($P < .001$) and 41.1% in the 45-mg arm ($P < .001$).

There were no reports of mucosal healing among patients in the placebo group. In contrast, mucosal healing occurred with all of the upadacitinib doses, at rates of 2.1% with 7.5 mg, 2.0% with 15 mg, 5.8% with 30 mg, and 14.3% with 45 mg. These differences did not achieve statistical significance vs placebo. In a post hoc analysis that defined mucosal healing as an endoscopic subscore of 1 or lower and a Geboes score of less than 2, the rates rose to 25.0% with upadacitinib at 45 mg (vs 0% with placebo; $P < .01$), 13.5% with 30 mg, and 16.3% with 15 mg ($P < .05$ for both comparisons with placebo).

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Long-Term Safety of Vedolizumab in Ulcerative Colitis and Crohn's Disease: Final Results From the GEMINI LTS Study

Dr Remo Panaccione presented the final results from the GEMINI LTS study (An Open-Label Study of Vedolizumab [MLN0002] in Participants With Ulcerative Colitis and Crohn's Disease Long-Term Safety) of vedolizumab in ulcerative colitis and Crohn's disease.¹ GEMINI LTS was a multinational, multicenter, open-label phase 3 study conducted between May 2009 and October 2017. The study enrolled roll-over patients from several studies: the phase 2 LTS (29 with ulcerative colitis and 8 with Crohn's disease), GEMINI 1 (675 with ulcerative colitis), GEMINI 2 (726 with Crohn's disease), and GEMINI 3 (384 with Crohn's dis-

ease). The study also enrolled de novo patients with ulcerative colitis (n=190) or Crohn's disease (n=231) who had not previously received treatment with vedolizumab. In GEMINI LTS, all patients received vedolizumab at 300 mg IV every 4 weeks. The primary endpoint of the study was long-term safety of vedolizumab in ulcerative colitis and Crohn's disease. Long-term efficacy was an exploratory endpoint. Interim analyses of efficacy from the GEMINI studies in both ulcerative colitis and Crohn's disease have previously been reported.^{2,3} Among patients with ulcerative colitis who responded to vedolizumab induction, the rates of remission were 88% after 104 weeks of

treatment and 96% after 152 weeks.² Among patients with Crohn's disease with a response at week 6 in GEMINI 2 who received vedolizumab continuously, the remission rates were 83% after 104 weeks and 89% after 152 weeks.³

The investigators noted that this final analysis represented the longest study to date of continuous treatment with vedolizumab. A total of 894 patients with ulcerative colitis and 1349 patients with Crohn's disease were included. For patients with ulcerative colitis, the mean age was 41.2 years, and the mean disease duration was 8.1 years. The mean partial Mayo score in patients with ulcerative

colitis was 6.0. Among patients with ulcerative colitis, previous treatments consisted of corticosteroids in 97%, immunomodulators in 74%, and anti-TNF agents in 46%. For patients with Crohn's disease, the mean age was 37.8 years, and the mean disease duration was 10.1 years. The mean Harvey-Bradshaw Index score was 1.9, and the mean Crohn's Disease Activity Index (CDAI) score was 314.0. In patients with Crohn's disease, prior treatments consisted of corticosteroids in 96%, immunomodulators in 86%, and anti-TNF agents in 67%. The median duration of exposure to vedolizumab was 43.0 months (range, 1 day to 113.7 months) in patients with ulcerative colitis and 31.9 months (range, 1 day to 101.7 months) in patients with Crohn's disease.¹

Among patients with ulcerative colitis, most adverse events were mild (18%) or moderate (50%) in severity. Severe events occurred in 24% of patients. An adverse event led 15% of patients with ulcerative colitis to discontinue treatment. The following adverse events were reported among this group: disease exacerbation (36% [105.2 incidence rate per 1000 patient-years]), nasopharyngitis (28% [93.9]), arthralgia (17% [51.6]), abdominal pain (12% [34.4]), upper respiratory tract infection (19% [55.7]), and headache (18% [55.5]). The rate of treatment-related adverse events in patients with ulcerative colitis was 40%.

Among patients with Crohn's disease, most adverse events were mild (17%) or moderate (49%). A severe event occurred in 31% of patients with Crohn's disease. A total of 17% of these patients discontinued treatment owing to an adverse event. The following adverse events were reported: disease exacerbation (35% [121.4 incidence rate per 1000 patient-years]), nasopharyngitis (25% [94.1]), arthralgia (24% [90.3]), abdominal pain (23% [80.0]), headache (21% [76.4]), and upper respiratory tract infection (16% [53.2]). The rate of treatment-related adverse events in patients with Crohn's disease was 46%.

ABSTRACT SUMMARY Long-Term Efficacy and Pharmacodynamics of the Anti-Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1) Monoclonal Antibody Ontamalimab (SHP647) in Crohn's Disease: the OPERA II Study

OPERA II was a multicenter, open-label, phase 2 extension study that evaluated the long-term safety and tolerability of ontamalimab in patients with moderate-to-severe Crohn's disease (Abstract OP08). Ontamalimab (SHP647) is a fully human monoclonal antibody that binds to MAdCAM-1, which is expressed on the intestinal endothelium. Ontamalimab inhibits the interaction between MAdCAM-1 and the $\alpha 4\beta 7$ integrin. Patients received ontamalimab at 75 mg SC every 4 weeks from baseline to week 72, and were followed for an additional 6 months. Dose de-escalation to 22.5 mg was permitted at the investigator's discretion. The remission rate remained relatively stable through the 72-week study in the 2 dose groups. Overall, 65.5% of patients who were not in remission at baseline achieved remission by the end of the study. In these patients, the median time to remission was 16.9 weeks. The most common treatment-emergent adverse event was Crohn's disease flares. Phase 3 clinical trials evaluating ontamalimab are under way.

Disease exacerbation was the most frequent serious adverse event, occurring in 13% of patients with ulcerative colitis and 17% of patients with Crohn's disease (Table 1). Treatment-related serious adverse events were reported in 4% of patients with ulcerative colitis and 6% of patients with Crohn's disease. Four patients with ulcerative colitis and 6 patients with Crohn's disease died during the study (a rate of 0.4% for each group).

Several adverse events of special interest were also examined. There were no cases of progressive multifocal leukoencephalopathy in either group of patients. Serious infections occurred in 7% of patients with ulcerative colitis and 11% of patients with Crohn's disease. The rate of *Clostridium difficile* infections was 1.7% vs 1.2%, respectively. Malignancies occurred in 6% vs 7%, infusion reactions in 4% vs 5%, and hepatic events in 3% vs 5%.

Rates of disease-related hospitalization, surgery, or another procedure (excluding colonoscopy) were 16.8% in the ulcerative colitis population and 28.1% in the Crohn's disease population. Among all patients, 10.0% (224 of 2244) underwent surgery. Among the patients who underwent surgery,

infectious complications occurred in 5 and serious complications in 10. Two of the serious complications were considered related to treatment.

Efficacy outcomes, an exploratory endpoint, were also briefly reported. The study investigators noted that the rates of clinical response and remission were similar in patients with ulcerative colitis or Crohn's disease. Response and remission were maintained long-term in patients who continued to receive vedolizumab. The study investigators noted that these analyses were limited by protocol-defined patient loss to follow-up (eg, owing to market approval or expanded-access program availability).

The investigators concluded that these results supported the safety and tolerability of vedolizumab for the long-term treatment of IBD.¹ Long-term use of vedolizumab did not increase the risk of clinically important safety concerns for patients with IBD, including progressive multifocal leukoencephalopathy, serious infections, or infusion reactions. The rates of arthralgia were consistent with those previously reported in the pivotal GEMINI studies. Patients in the GEMINI LTS study showed evidence of continued

Table 1. Serious Adverse Events in the GEMINI LTS Study of Vedolizumab in Ulcerative Colitis and Crohn's Disease

	Ulcerative Colitis (n=894)		Crohn's Disease (n=1349)	
	n ^a (%)	Incidence rate per 1000 patient-years ^b	n ^a (%)	Incidence rate per 1000 patient-years ^b
Serious adverse events	277 (31)	90.9	548 (41)	146.5
Disease exacerbation	119 (13)	34.8	224 (17)	50.3
Abdominal pain	9 (1)	2.6	41 (3)	9.0
Anal abscess	0	0	33 (2)	7.3
Small intestinal obstruction	4 (<1)	1.1	25 (2)	5.5
Treatment-related serious adverse events	37 (4)	NA	79 (6)	NA
Deaths	4 (0.4) ^c	NA	6 (0.4) ^d	NA
Treatment-related deaths	1 (0.1) ^e	NA	1 (0.1) ^f	NA

GEMINI LTS, An Open-Label Study of Vedolizumab (MLN0002) in Participants With Ulcerative Colitis and Crohn's Disease Long-Term Safety; NA, not available.

^aValues are the number of patients with an event.

^bTime-adjusted incidence rate per 1000 patient-years = (Number of patients experiencing an adverse event of interest/total person-time in years) × 1000.

^cRespiratory failure, acute stroke, West Nile virus encephalitis, pulmonary embolism.

^dTraumatic intracranial hemorrhage, hepatocellular carcinoma, suicide, pneumonia, septicemia, leiomyosarcoma.

^eWest Nile virus encephalitis.

^fHepatocellular carcinoma.

Adapted from Vermeire S et al. ECCO abstract OP26. *J Crohns Colitis*. 2019;13(suppl 1).¹

efficacy with vedolizumab. These final data were consistent with the known safety profile of vedolizumab previously reported in published clinical trials and real-world studies.²⁻⁶

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Pediatric Crohn's Disease Adalimumab Level-Based Optimization Treatment (PAILOT) Randomized Controlled Trial

Dr Amit Assa and coworkers presented the efficacy results from the PAILOT trial (Pediatric Crohn's Disease Adalimumab Level-Based Optimization Treatment), a nonblinded, randomized controlled study of adalimumab among pediatric patients with Crohn's disease.¹ PAILOT aimed to determine whether rates of clinical remission were improved with proactive vs reactive measurement of drug levels. With the proactive strategy,

therapeutic drug monitoring was used to maintain serum levels of adalimumab above 5 µg/mL. With the reactive strategy, drug levels were measured when clinically indicated. The primary endpoint was sustained corticosteroid-free clinical remission (Pediatric Crohn's Disease Activity Index score <10) during the study period (weeks 8-72).

The study population consisted of 78 children (ages 6-17 years) with luminal Crohn's disease. The patients had

not received previous treatment with a biologic therapy. They had responded to adalimumab induction at week 4. The study randomly assigned patients into proactive and reactive groups. In the proactive group, trough adalimumab concentrations were measured at weeks 4 and 8, and then every 8 weeks thereafter until week 72. The dose of adalimumab was adjusted (when <40 mg) or treatment intervals were modified to maintain drug levels of 5 µg/mL

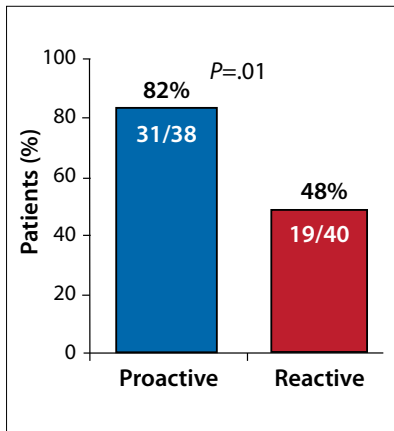


Figure 6. Sustained corticosteroid-free remission (PCDAI <10) among children with Crohn's disease treated with adalimumab in the PAILOT trial. PAILOT, Pediatric Crohn's Disease Adalimumab Level-Based Optimization Treatment; PCDAI, Pediatric Crohn's Disease Activity Index. Adapted from Assa A et al. ECCO abstract OP18. *J Crohns Colitis*. 2019;13(suppl 1).¹

or higher. In the reactive group, physicians were informed of the trough levels only when clinically indicated, based on symptoms or elevated levels of C-reactive protein (CRP) or fecal calprotectin. The dose or treatment intervals of adalimumab were then adjusted based on the trough levels.

The rate of sustained corticosteroid-free remission (weeks 8-72) was 82% in the proactive group vs 48% in the reactive group ($P<.01$; Figure 6). The rate of a sustained CRP level of 0.5 mg/dL or lower (weeks 8-72) was 74% vs 57%, a difference that was not statistically significant ($P=.11$). A significant difference was seen with the

rates of a sustained fecal calprotectin level of 150 $\mu\text{g/g}$ or lower, at 47% in the proactive arm vs 22% in the reactive arm ($P=.02$). The composite outcome for these 2 measurements was 42% vs 12% ($P=.003$).

Proactive measurements reduced the risk for mild exacerbations, but not for moderate to severe exacerbations. The patients who underwent proactive measurement had a higher rate of adalimumab intensifications (primarily early in the study) and longer periods in which the defined adalimumab trough thresholds were exceeded. The overall rates of adverse events between the 2 groups were similar (13% in the proactive group and 15% in the reactive group).

The investigators noted limitations to the study, such as the nonblinded design and the lack of endoscopic assess-

ment.¹ They concluded that pediatric patients with Crohn's disease undergoing treatment with adalimumab may benefit from proactive monitoring of trough adalimumab levels. However, they acknowledged that proactive monitoring had no significant effect on the rate of severe exacerbations. They concluded that intensification of adalimumab should be considered a standard strategy, particularly for early optimization of trough adalimumab concentrations.

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Maintenance Treatment With Mirikizumab, a P19-Directed IL-23 Antibody: 52-Week Results in Patients With Moderately to Severely Active Ulcerative Colitis

Dr Geert R. D'Haens and colleagues presented the results of a phase 2 trial of maintenance treatment with mirikizumab, a humanized p19-directed interleukin (IL) 23 antibody.¹ The study randomly

assigned patients to receive placebo or mirikizumab at 1 of 3 doses: 50 mg with the possibility of exposure-based dose increases, 200 mg with the possibility of exposure-based dose increases, or 600 mg at a fixed dose. Data from

the induction period of the study were previously reported, showing efficacy and tolerability at week 12 in patients with moderately to severely active ulcerative colitis.² The rates of clinical remission were 4.8% with placebo

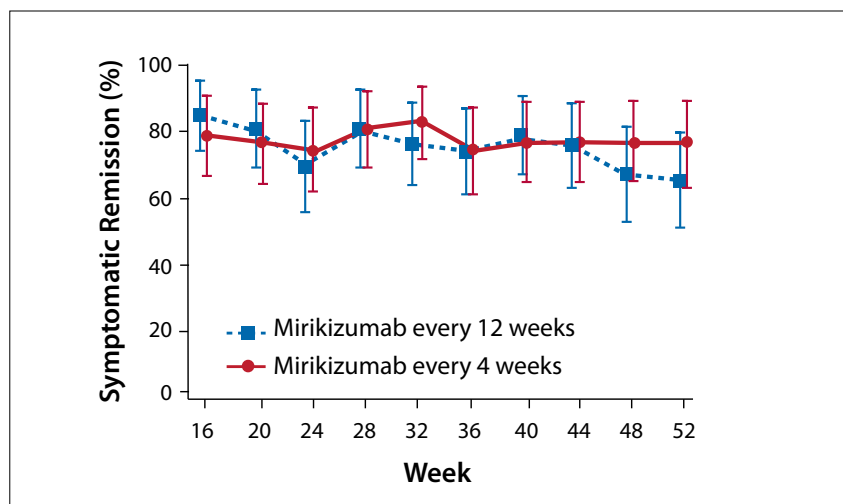


Figure 7. Symptomatic remission among patients with ulcerative colitis who received maintenance treatment with mirikizumab. The 95% CIs are shown. Symptomatic remission was defined as stool frequency of 0 or 1 and rectal bleeding of 0 according to modified Mayo scores. Adapted from D'Haens GR et al. ECCO abstract OP38. *J Crohns Colitis*. 2019;13(suppl 1).¹

ABSTRACT SUMMARY Effectiveness and Safety of Ustekinumab 90 Mg Every 4 Weeks in Crohn's Disease

A retrospective cohort study evaluated the safety and efficacy of ustekinumab at 90 mg administered every 4 weeks (Abstract OP24). The study enrolled patients who had an incomplete response or loss of response after treatment with ustekinumab administered at the dose approved by the US Food and Drug Administration: 90 mg every 8 weeks. The study included 87 patients with active Crohn's disease who had at least 1 objective sign of inflammation (elevated CRP, elevated fecal calprotectin, and/or radiologic or endoscopic evidence of disease activity). Seventy percent of the patients had an incomplete response with the original regimen, and the remaining 30% lost response. After treatment with ustekinumab at 90 mg every 4 weeks, 55% of patients had an immediate response, defined as an improvement of symptoms at the first clinic visit after dose intensification (median time of evaluation, 2.1 months), as determined by the treating physician. At this immediate evaluation, 31% of patients achieved a clinical remission. At the end of follow-up (median, 8.2 months), 33% of patients had a sustained response, and 24% of patients were in a corticosteroid-free clinical remission.

compared with 15.9% in the 50-mg arm ($P=.066$), 22.6% in the 200-mg arm ($P=.004$), and 11.5% in the 500-mg arm ($P=.142$).

During the maintenance phase of the study, the objective was to determine the efficacy and safety of maintenance mirikizumab in patients who responded to 12 weeks of induction therapy.¹ Endpoints were measured at week 52. At week 12, patients ($n=93$)

who responded to induction therapy were randomly assigned to maintenance treatment with mirikizumab at 200 mg every 12 weeks (q12w) or every 4 weeks (q4w). Baseline demographics were balanced between these 2 arms. Notably, no prior biologic therapy exposure was reported in 50.0% of the q12w arm and 44.7% of the q4w arm. One prior biologic therapy was reported in 37.0% vs

25.5%. At baseline, concomitant therapies included 5-aminosalicylate acid (87.0% in the q12w arm vs 78.7% in the q4w arm), corticosteroids (41.3% vs 46.8%), and thiopurines (19.6% vs 31.9%).

The rate of clinical remission at week 52 was 37.0% with mirikizumab q12w and 46.8% with mirikizumab q4w (Figure 7). A subgroup analysis evaluated outcome according to prior treatment with a biologic therapy. The rates of clinical remission were 36.0% in the q12w arm vs 47.8% in the q4w arm among the biologic-naïve patients and 38.1% vs 46.2%, respectively, among those previously treated with biologic therapy. The rates of clinical remission at both weeks 12 and 52 were 38.5% in the q12w arm and 61.6% in the q4w arm. Among patients with a clinical response at week 12, the rates of clinical remission at week 52 were 36.4% in the q12w arm and 37.9% in the q4w arm.

Endoscopic healing was seen in 47.8% of the q12w arm and 57.4% of the q4w arm. Endoscopic remission was reported in 28.3% vs 14.9%.

A treatment-emergent adverse event occurred in 67.4% of patients in the q12w arm and 76.6% of patients in the q4w arm. The most common of these events in the q12w arm consisted of nasopharyngitis (15.2%), worsening of ulcerative colitis (15.2%), and headache (6.5%). Arthralgia (12.8%), nasopharyngitis (10.6%), headache (10.6%), and upper respiratory tract infections (10.6%) were the most common treatment-emergent adverse events in the q4w arm. Adverse events led to treatment discontinuation in 2.2% of the q12w arm and no patients in the q4w arm.

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Real-World Effectiveness and Safety of Vedolizumab and Anti-TNF Therapy in Biologic-Naive Patients With Ulcerative Colitis or Crohn's Disease: Results From the EVOLVE Study

Two studies reported outcomes from EVOLVE, a multicountry, multicenter, retrospective chart review study that evaluated the real-world safety and efficacy of vedolizumab and anti-TNF agents. Patients in the study were naive to biologic therapy at initiation of vedolizumab or anti-TNF therapy during the eligibility period (May 2014 to July 2017) and had at least 6 months of follow-up data.^{1,2}

Dr Andres Yarur and colleagues reported on outcomes among patients with ulcerative colitis in the EVOLVE study.³ Among the 527 patients with ulcerative colitis, 325 initiated treatment with vedolizumab and 202 with an anti-TNF agent. Throughout the first 24 months of treatment, 75.1% of the vedolizumab group remained on treatment vs 53.8% of the anti-TNF therapy group ($P < .01$). The most common reasons for treatment discontinuation included primary nonresponse (11.1% for vedolizumab vs 16.3% for anti-TNF therapy) and secondary loss of response (8.4% vs 9.4%). A dose escalation in the initial 24 months of treatment was required by 24.7% of the vedolizumab group vs 30.5% of the anti-TNF therapy group (unadjusted $P < .05$).

Among evaluable patients, clinical outcomes at 24 months were similar between the treatment groups. A clinical response was seen in 90.8% of the vedolizumab arm and 85.7% of the anti-TNF therapy arm ($P = .82$). Rates of clinical remission were 79.0% vs 66.2% ($P = .37$). Mucosal healing occurred in 92.0% vs 84.4% ($P = .67$). After adjustment for baseline confounders, there were no significant differences in these clinical outcomes. After adjustment, disease exacerbation was less common with vedolizumab vs the anti-TNF therapy (HR, 0.7; 95% CI, 0.5-0.9). However, the rate of colectomies did not differ between the

treatment groups.

After adjustment for baseline confounders, serious adverse events were less common with vedolizumab vs anti-TNF therapy (HR, 0.5; 95% CI, 0.3-0.8). The most frequent serious adverse event was anemia in the vedolizumab arm (12.0%) and pain in the anti-TNF therapy arm (12.0%). The rates of serious infections were similar between the treatment groups.

Dr Brian Bressler and colleagues reported on patients with Crohn's disease in the EVOLVE study.⁴ Among the 419 patients with Crohn's disease, 177 initiated treatment with vedolizumab and 242 began treatment with an anti-TNF agent. More patients in the vedolizumab arm remained on treatment at 12 months (85.6% vs 76.0% in the anti-TNF arm; $P = .02$) and 18 months (78.8% vs 70.2%; $P = .04$). At 24 months, the difference was not statistically significant (71.4%

vs 70.7%; $P = .11$). The most common reasons for treatment discontinuation with vedolizumab were primary nonresponse (9.0%) and secondary loss of response (4.0%). Among patients in the anti-TNF agent arm, the primary reasons for treatment discontinuation were nonserious adverse events (6.7%) and primary nonresponse (4.6%). Throughout a 24-month period, the cumulative probability for dose escalation was similar for patients treated with vedolizumab or an anti-TNF agent.

A comparison of clinical outcomes at 12, 18, and 24 months is shown in Figure 8. Clinical outcome at 24 months was similar between the treatment groups. A clinical response was seen in 74.5% of the vedolizumab arm vs 73.4% of the anti-TNF therapy arm. A clinical remission occurred in 69.7% vs 66.4% ($P = .80$). Mucosal healing was reported in 100% vs 90.1%

ABSTRACT SUMMARY A Vedolizumab Specific 4-Gene Colonic Signature Accurately Predicting Future Endoscopic Remission in Patients With Inflammatory Bowel Disease

A study by Dr Bram Verstockt and colleagues aimed to identify baseline transcriptomic profiles in inflamed colonic tissue of patients with IBD that could predict the likelihood of future endoscopic remission with vedolizumab (Abstract DOP38). This study defined endoscopic remission as a Mayo endoscopic score of 0 or 1 in patients with ulcerative colitis, and as the absence of ulcerations in patients with Crohn's disease. The study evaluated 31 colonic biopsies from patients who then initiated treatment with vedolizumab. In addition, 24 colonic biopsies from patients who initiated treatment with anti-TNF therapy were evaluated for comparison. The study identified 44 genes that were differentially expressed in the biopsies of patients who did vs did not achieve endoscopic remission after treatment with vedolizumab. From these genes, a 4-gene signature was identified that could accurately identify patients who did or did not achieve vedolizumab-induced endoscopic remission. This same 4-gene signature was applied to a publicly available data set of 13 vedolizumab-treated patients, and it accurately identified those patients who did or did not achieve endoscopic remission. The 4-gene signature was specific to vedolizumab-induced endoscopic remission; it did not predict remission among patients treated with anti-TNF therapy.

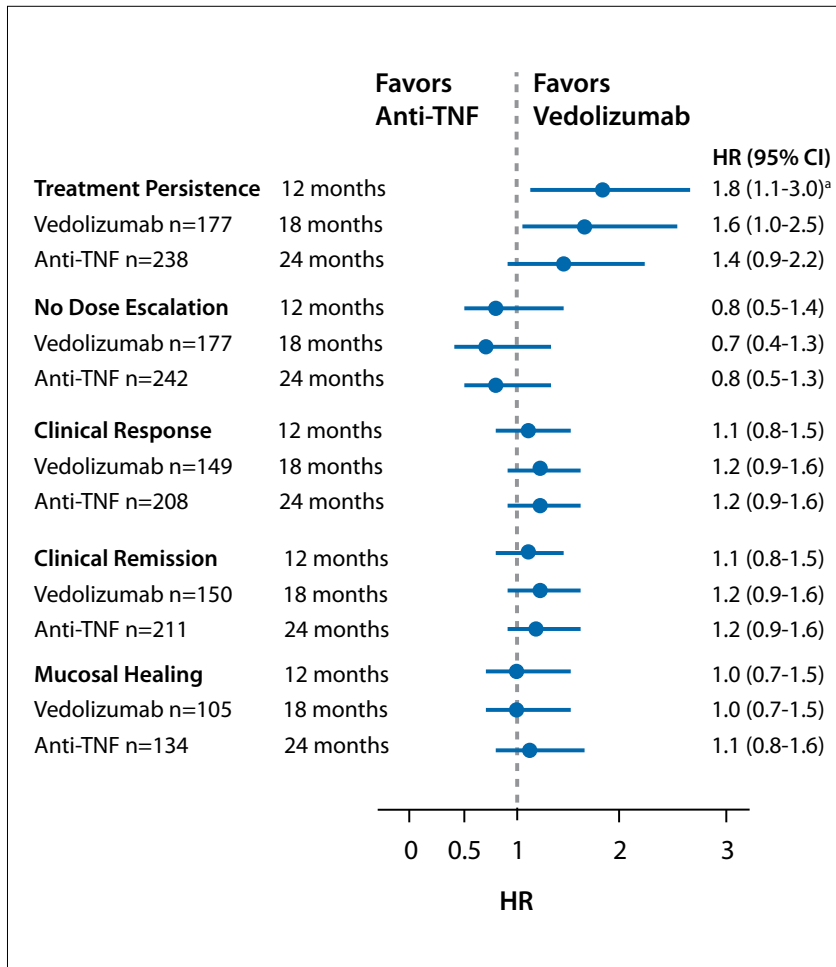


Figure 8. Adjusted hazard ratios for treatment patterns and clinical effectiveness for vedolizumab vs anti-TNF agents among patients with biologic-naïve Crohn's disease. ^aDenotes a significant difference between vedolizumab and anti-TNF therapy based on an adjusted Cox proportional hazards model. HR, hazard ratio; TNF, tumor necrosis factor. Adapted from Bressler B et al. ECCO abstract P621. *J Crohns Colitis*. 2019;13(suppl 1).⁴

($P=.82$). After adjustment for baseline confounders, there were no significant differences in these clinical outcomes.

There were no significant differences in the rates of disease exacerbation or disease-related surgery between the groups after adjustment for baseline confounders. Rates of serious adverse events and serious infections were not significantly different after adjustment. Among vedolizumab-treated patients, the most common serious adverse event was small bowel obstruction (28.6%). Among patients who received an anti-TNF agent, gastrointestinal (GI) infection (17.0%) was the most frequent serious adverse event.

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A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of a Targeted-Release Oral Cyclosporine Formulation in the Treatment of Mild to Moderate Ulcerative Colitis: Efficacy Results

Dr Stuart Bloom and coworkers reported on the preliminary results from a randomized, multicenter, double-blind, placebo-controlled study designed to evaluate the benefit of a targeted-release oral cyclosporine formulation in patients with mild-to-moderate ulcerative colitis.¹ This novel formulation, known as ST-0529, incorporates polymer-coated multiparticulate beads and is designed

for the targeted release of the cyclosporine drug in the ileum and colon to avoid systemic absorption. A phase 1 dose-ranging study determined that twice daily dosing of ST-0529 improved colonic tissue concentrations of cyclosporine.²

The study by Dr Bloom included 118 patients with a baseline modified Ulcerative Colitis Disease Activity Index (mUCDAI) of 4 to 10 and a

diagnosis of either mild (mUCDAI score <6) or moderate (mUCDAI score ≥6) disease.¹ Exclusion criteria included severe or fulminant ulcerative colitis and rectum-limited disease. Patients were also excluded if they had received treatment with topical therapies, corticosteroids at 10 mg/day or higher within the 4 weeks before study initiation, or biologic therapies in the 2 months before the start of the

study. Treatment with concomitant medications was permitted. At baseline, the mean total patient mUCDAI score was 7.2 ± 1.81 in the ST-0529 arm vs 7.5 ± 1.72 in the placebo arm. The mean disease duration was 6.14 ± 5.47 years vs 9.60 ± 7.51 years, respectively.

All patients received 4 weeks of treatment with ST-0529 (75 mg/day) or placebo. The study design included reassessment during a follow-up visit at week 8. The primary study endpoint was clinical remission, defined as an mUCDAI score of 2 or lower, with no individual score higher than 1 and a rectal bleeding subscore of 0 or 1. Secondary study endpoints included clinical response, mucosal and histologic healing, and safety and tolerability. Clinical response was defined as a reduction in the mUCDAI score of 3 or higher at week 4, with a decrease in the rectal bleeding subscore of 1 or more or with an absolute rectal bleeding subscore of 0 or 1.

At the time of this preliminary analysis, the rates of study discontinuation were 18.9% with ST-0529 vs 35.4% with placebo. Among patients in the ST-0529 arm, the primary reasons for discontinuation were an adverse event (11.3%) and lack of efficacy (7.5%). In the placebo arm, more patients discontinued owing to an adverse event (24.6%), and a similar proportion discontinued owing to a lack of efficacy (7.7%).

In the overall population, clinical remission occurred in 13.2% of the ST-0529 arm vs 6.3% of the placebo arm; this difference was not statistically

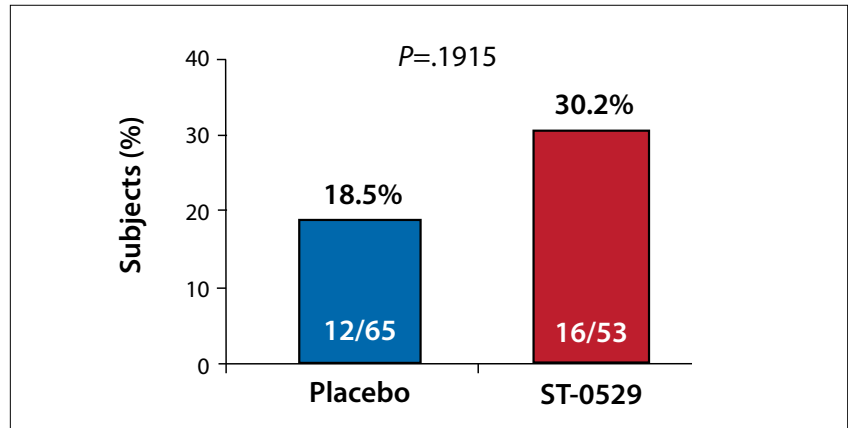


Figure 9. Response rates among patients with ulcerative colitis treated with ST-0529 or placebo. Response was defined as a reduction in the mUCDAI score of ≥ 3 at week 4 with a decrease in the rectal bleeding subscore of ≥ 1 , or with an absolute rectal bleeding subscore of 0 or 1. mUCDAI, modified Ulcerative Colitis Disease Activity Index. Adapted from Bloom S et al. ECCO abstract OP16. *J Crohns Colitis*. 2019;13(suppl 1).¹

significant ($P=.2175$). The rate of response was 30.2% with ST-0529 vs 18.5% with placebo, but this difference was also not statistically significant ($P=.1915$; Figure 9). A post hoc analysis examined response among the 93 patients with moderate disease. The response rate was 35.0% with ST-0529 vs 17.0% with placebo ($P=.0499$).

Adverse events deemed treatment-related as well as treatment-emergent occurred in 20.8% of the ST-0529 arm vs 27.7% of the placebo arm. Treatment-emergent serious adverse events occurred in 9.4% vs 7.7%.

The investigators mentioned several limitations to this study, including an imbalance in the randomization of patients between the placebo and ST-0529 arms and the short duration of treatment (4 weeks). No data were

collected at the week 8 follow-up. There was early discontinuation within the first 2 weeks of the study. The investigators further noted that the formulation of ST-0529 has since been optimized, and a new formulation of the drug is under evaluation in an ongoing phase 2 trial.³

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Real-World Analyses of IBD Patients Treated With Vedolizumab

A retrospective study compared treatment patterns and health care resource utilization among biologic-naïve patients with IBD initiating treatment with infliximab or vedolizumab in the United States.¹ The observational analysis included 1068 patients with IBD, of whom 27.3% were treated with vedolizumab and

72.7% with infliximab. At 12 months, the rates of treatment persistence were 86.8% with vedolizumab vs 77.7% with infliximab ($P=.0099$). Similar results were observed at 24 months, at 79.6% vs 62.4% ($P=.0006$). Among patients with ulcerative colitis, the rate of treatment persistence at 24 months was 81.5% with vedolizumab

vs 65.4% with infliximab, a difference that was not statistically significant ($P=.1354$). A significant difference was seen for treatment persistence among patients with Crohn's disease, at 78.1% vs 66.0% ($P=.0437$). Overall, the rate of increased dosing frequency was 8.4% with vedolizumab vs 14.4% with infliximab ($P=.05$)

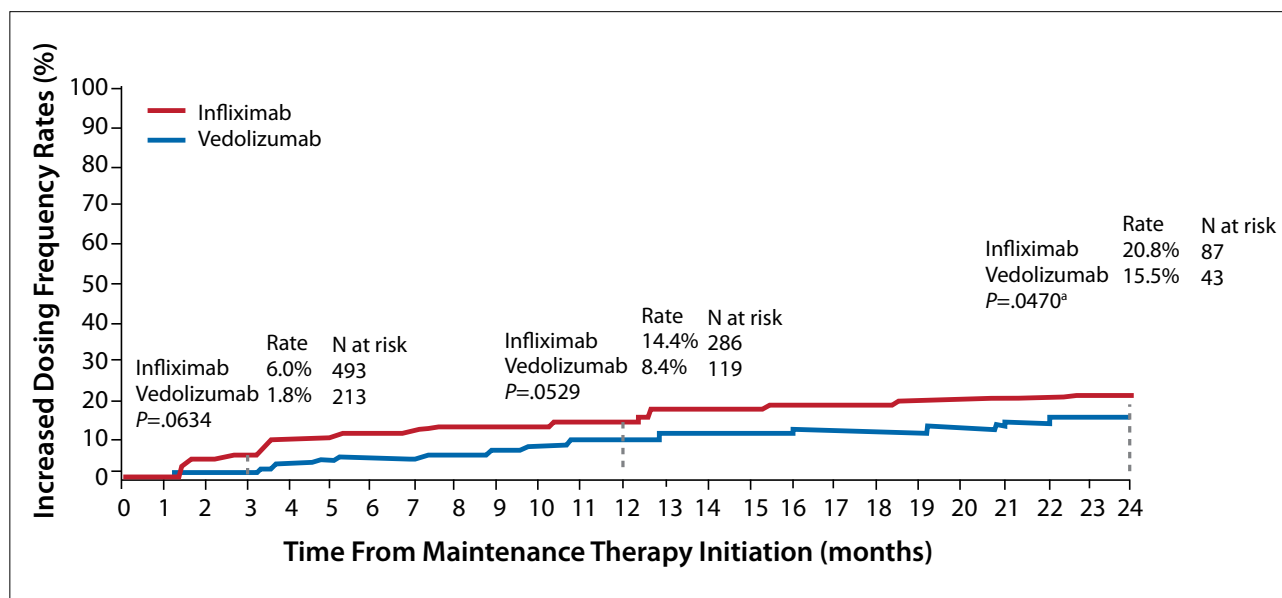


Figure 10. Increased dosing frequency among patients with inflammatory bowel disease treated with vedolizumab or infliximab. *Statistically significant at the 5% level. Adapted from Latremouille-Viau D et al. ECCO abstract P379. *J Crohns Colitis*. 2019;13(suppl 1).¹

at 12 months, and 15.5% vs 20.8% ($P < .0470$) at 24 months (Figure 10). The rate of increased dosing frequency at 24 months was highest among patients with ulcerative colitis treated with infliximab, at 24.1% (vs 10.9% in the vedolizumab arm). Among patients with Crohn's disease, the rate of increased dosing frequency at 24 months was 17.9% in the infliximab arm vs 18.5% in the vedolizumab arm. The 24-month rates of health care resource utilization were 54.0% with vedolizumab vs 58.9% with infliximab ($P = .0457$).

A retrospective cohort study from Singapore analyzed patients treated with vedolizumab.² Among the 25 patients with ulcerative colitis, the rates of corticosteroid-free clinical remission at weeks 14, 24, and 54 were 68.0%, 66.7%, and 80.0%, respectively. Among the 28 patients with Crohn's disease, these rates were 42.9%, 45.0%, and 46.2%. After a median treatment duration of 31 weeks, endoscopic remission was reported in 35.3% of patients with ulcerative colitis and 30.8% of patients with Crohn's disease. The radiologic remission rate

(documented in Crohn's disease only) was 22.2%. Treatment was discontinued by 7 patients with Crohn's disease and 6 with ulcerative colitis. An adverse event occurred in 47.2% of patients. The most common adverse event was infection (37.7%). No malignancies or deaths were reported.

A prospective cohort study from Korea evaluated patients with either Crohn's disease or ulcerative colitis who initiated treatment with vedolizumab after an inadequate response to anti-TNF therapy.³ The co-primary outcomes of the study were corticosteroid-free clinical remission at week 14 (for both ulcerative colitis and Crohn's disease patients) and endoscopic remission and response at weeks 53 to 57 (for ulcerative colitis patients).

Among the 18 patients with ulcerative colitis, at week 14, the rate of corticosteroid-free clinical remission was 16.7%, and the rate of corticosteroid-free clinical response was 38.9%. In the 35 patients with Crohn's disease, these rates were 38.9% and 33.3%, respectively. At weeks 53 to 57, the rates of corticosteroid-free clinical remission were 28.6% in

patients with ulcerative colitis and 60.0% in those with Crohn's disease. The rates of corticosteroid-free clinical response were 42.9% and 60.0%. Among patients with ulcerative colitis, the Mayo Endoscopic Score–defined endoscopic remission rate at weeks 53 to 57 was 33.3%, and the Mayo Endoscopic Score–defined endoscopic response rate was 50%.

A serious adverse event occurred in 30.2% of the cohort, and 15.1% discontinued vedolizumab owing to a poor response. Adverse events included nasopharyngitis (24.5%), arthralgia (22.6%), and headache (22.6%).

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Highlights in IBD From the 14th Congress of ECCO: Commentary

Edward V. Loftus Jr, MD

Presentations at the 14th Congress of the European Crohn's and Colitis Organisation (ECCO) provided important, practice-changing insights into the management of inflammatory bowel disease (IBD).

Vedolizumab

In many ways, the phase 3b VARSITY trial of vedolizumab vs adalimumab was the most important study presented at the congress. Dr Stefan Schreiber and colleagues provided the results of this late-breaking abstract.¹ VARSITY is the first trial to compare 2 biologic therapies for IBD. Previously, when evaluating data for biologic therapies, it was necessary to rely on cross-trial comparisons or network meta-analyses. Head-to-head, randomized controlled trials provide the highest level of evidence when comparing treatments. VARSITY used a "treat-straight-through" design; in other words, patients were not re-assigned to a different treatment arm. All patients continued treatment with their initial therapy, so this trial was more rigorous than those that permit patients to cross over to a different treatment. Results favored vedolizumab over adalimumab for the primary endpoint of clinical remission. These rates were 31.3% for vedolizumab vs 22.5% for adalimumab ($P=0.0061$). Vedolizumab also improved a major secondary endpoint, "mucosal healing" or endoscopic improvement. These rates were 39.7% with vedolizumab vs 27.7% with adalimumab ($P=0.0005$). (The study used the term "mucosal healing." However, the better current term is "endoscopic improvement," because the US Food and Drug Administration [FDA] has now suggested that the term "mucosal healing" should not be used to describe an endoscopic endpoint without an accompanying histologic endpoint.²) The rates of adverse events were approximately the same for both treatments. Numerically, there were fewer overall infections with vedolizumab.

Results from the VARSITY trial will likely influence many practitioners. Vedolizumab appears to have moderate superiority vs adalimumab in ulcerative colitis, and it should be considered a first-line biologic therapy.

The GEMINI LTS study evaluated long-term safety results with vedolizumab.³ In the GEMINI 1 and GEMINI 2 trials, vedolizumab was shown to be effective for Crohn's disease and ulcerative colitis.^{4,5} This study of long-term safety included patients who "rolled over" from multiple vedolizumab clinical trials, as well as de novo patients with IBD. Patients were treated with an every-4-week regimen. Some patients had been receiving treatment for up to 5 years. The final results of the study showed that vedolizumab was both safe and effective, and that many of the patients were able to continue treatment for an extended period. The annualized rates of serious adverse events were approximately 9% among patients with ulcerative colitis and 14.6% among those with Crohn's disease; however, rates were much lower when limiting the serious adverse events to those that the investigators deemed related to treatment. The annualized rate of serious infections was 1.8% among ulcerative colitis patients and 3.4% among Crohn's disease patients, and there were no cases of progressive multifocal leukoencephalopathy. There were 2 deaths that were deemed by the investigators to be treatment-related (from West Nile virus encephalitis and hepatocellular carcinoma). Overall, this long-term study showed that vedolizumab has a favorable safety profile with good efficacy.

A post hoc analysis of the GEMINI trials focused on whether early disease control with vedolizumab impacts rates of surgery.⁶ This analysis was based on data from the GEMINI-2 and GEMINI LTS studies.^{3,5} Results were stratified according to disease duration. A previously developed clinical

decision support tool had been shown to be somewhat predictive of whether a patient with Crohn's disease would respond to vedolizumab.⁷ Surgical rates were twice as high among patients with a low probability of response to vedolizumab vs those with a high probability of response (12.9% vs 6.0%). Among patients with a low probability of response, using a cutoff of 5 years' disease duration, those patients with a shorter duration of disease before treatment had lower rates of surgery than patients with a longer duration. Therefore, among patients with a shorter duration of disease, it may be possible to use vedolizumab regardless of what their predicted probability of response appears to be at baseline.

The VISIBLE trials evaluated whether vedolizumab would be effective when administered as a subcutaneous formulation; the top-line results were presented at the 2018 United European Gastroenterology (UEG) Week.⁸ The patients began treatment with 2 doses of open-label intravenous vedolizumab at weeks 0 and 2. At week 6, patients with a clinical response were randomly assigned to maintenance treatment with the intravenous formulation at 300 mg every 3 weeks, the subcutaneous formulation at 108 mg every 2 weeks, or a matching placebo. Results presented at earlier meetings showed that subcutaneous administration was equivalent to intravenous administration in regard to efficacy and safety.⁸ An analysis by Dr Séverine Vermeire and colleagues evaluated quality of life and work productivity among patients with ulcerative colitis.⁹ The analysis showed significant improvements with vedolizumab, both subcutaneous and intravenous, compared with placebo for the Inflammatory Bowel Disease Questionnaire, the EuroQol 5D Visual Analogue Scale, and the Work Productivity and Activity Impairment questionnaire. These data provide secondary evidence of the benefits associated with vedolizumab.

Patients' quality of life was improved, and they were able to go back to work.

I was the first author on an abstract that assessed response to 2 or 3 doses of open-label intravenous vedolizumab.¹⁰ Patients underwent evaluation at week 6. There was no placebo control because the analysis took place before patients were randomly assigned to therapy, when the treatment consisted of open-label intravenous vedolizumab. The overall response rates at week 6 were 56% in patients with ulcerative colitis and 64% in those with Crohn's disease. Among patients who received a third intravenous infusion, these rates were even higher, at 79% and 63%. After 2 or 3 infusions, a clinical response was seen in 86% of patients with ulcerative colitis and 82% of those with Crohn's disease. These data show that vedolizumab is effective, and that the drug begins to work by week 6 in many patients. Among patients without a clinical response at week 6, another dose at this time can lead to a response by week 14.

The EVOLVE study retrospectively examined real-world data for patients with ulcerative colitis treated with vedolizumab or anti-tumor necrosis factor (TNF) therapy.¹¹ Approximately 3 and a half years of data on efficacy and safety were gathered from 37 different centers. Patients had not received previous treatment with biologic therapy. The EVOLVE study was not a head-to-head trial, but it does provide some insights. There were differences between the 2 groups. Patients treated with anti-TNF agents were somewhat younger, and they had a shorter disease duration. They had higher levels of C-reactive protein. There were more hospitalizations among patients with ulcerative colitis in the anti-TNF-treated group. However, rates of overall response, remission, and mucosal healing were similar in both groups. The rate of treatment persistence (meaning the duration of treatment) was higher among patients treated with vedolizumab vs anti-TNF therapy. At 24 months, 75.1% of patients continued treatment with vedolizumab vs 53.8% with anti-

TNF therapy ($P < .01$). Patients treated with vedolizumab were significantly less likely than the anti-TNF-treated patients to develop exacerbation of ulcerative colitis (28.3% vs 43.9%) or serious adverse events (4.9% vs 10.4%). These real-world data therefore suggest that the efficacy of vedolizumab is equivalent, or even slightly superior, to that of anti-TNF agents. In terms of safety, vedolizumab is better than the anti-TNF agents. The EVOLVE study suggests that vedolizumab can be used as a first-line biologic agent for ulcerative colitis.

A separate analysis of the EVOLVE study evaluated patients with Crohn's disease who had not yet received treatment with a biologic therapy.¹² Treatment persistence was better with vedolizumab than anti-TNF therapy at 12 months, but there were no differences at 18 and 24 months. The rates of exacerbation of Crohn's disease and of surgeries, serious adverse events, and infections related to Crohn's disease were numerically lower with vedolizumab, but the differences were not statistically significant. These data again show that vedolizumab is comparable to anti-TNF agents and therefore should be considered a reasonable treatment choice in biologic-naïve patients. In my own practice, when treating a Crohn's disease patient with fistulizing disease, I would choose an anti-TNF agent first because there are more data supporting the efficacy of this approach.¹³ However, in a patient with luminal inflammatory disease, vedolizumab is a reasonable option.

Ustekinumab

The UNIFI trial evaluated ustekinumab in patients with ulcerative colitis. Data from the induction phase, presented at the 2018 UEG Week, were positive for the 2 regimens tested.¹⁴ Dr William J. Sandborn and colleagues presented data from the maintenance phase.¹⁵ The responders in UNIFI were randomly assigned to treatment with either placebo or ustekinumab at subcutaneous doses of 90 mg administered every 12 weeks or every 8 weeks. The primary

endpoint, clinical remission (Mayo score, ≤ 2 ; with no subscore > 1) at week 44, was met. Both doses of ustekinumab significantly improved clinical remission vs placebo; the difference between ustekinumab and placebo ranged from 14% to 19%, which is reasonable. Ustekinumab also significantly improved secondary endpoints, such as clinical response and endoscopic improvement. (I would not characterize this improvement as "endoscopic healing.") The FDA is currently evaluating ustekinumab for ulcerative colitis.

A French multicenter study evaluated patients with Crohn's disease treated with ustekinumab who required dose escalation to 90 mg every 4 weeks because of incomplete clinical response or loss of response.¹⁶ In more than half of patients, this dose escalation was able to recapture clinical response in the short-term, and it was safe. This strategy is off-label, but it may provide a good option for patients with refractory Crohn's disease.

Novel Treatments

Dr William J. Sandborn presented the results of a secondary analysis of the induction data for U-ACHIEVE, a trial of upadacitinib in ulcerative colitis.¹⁷ Upadacitinib is a second-generation Janus kinase (JAK) inhibitor. The first JAK inhibitor in IBD was tofacitinib for ulcerative colitis. Tofacitinib inhibits JAK1 and JAK3, and, to a lesser extent, JAK2. In contrast, upadacitinib is a selective JAK1 inhibitor. Theoretically, this specificity might translate into better safety and efficacy outcomes. A previous phase 2 trial in Crohn's disease suggested that upadacitinib was superior to placebo.¹⁸ The U-ACHIEVE trial is the first study of upadacitinib in ulcerative colitis. The top-line induction results were presented at the 2018 UEG Week.¹⁹ At ECCO this year, Dr Sandborn presented the endoscopic and histologic data.¹⁷ The top 2 doses of upadacitinib, 45 mg/day and 30 mg/day, were associated with statistically significant improvements vs placebo for several endoscopic outcomes, including improvement (Mayo endoscopic sub-

score, 0-1) and remission (Mayo endoscopic subscore, 0). The top 3 doses of upadacitinib, 45 mg/day, 30 mg/day, and 15 mg/day, were associated with statistically significant higher rates of histologic improvement (any decrease from baseline in the Geboes score) and histologic remission (Geboes score, <2). This study incorporated the new definition of mucosal healing as consisting of both endoscopic improvement and histologic remission. The mucosal healing endpoint was significantly higher for the top 2 doses of upadacitinib (25% and 13.5%, vs 0% for placebo). These data corroborate the clinical remission data, which were also positive. Endoscopic and histologic improvements are more objective markers of improvement than symptoms. Overall, the data from this study suggest that upadacitinib has efficacy for ulcerative colitis. Results for maintenance treatment are forthcoming. It will be helpful to have a drug with yet another mechanism of action for both ulcerative colitis and Crohn's disease.

Mirikizumab is one of many interleukin (IL)-23 antibodies in development for IBD; the others include risankizumab and brazikumab. In comparison to ustekinumab, which blocks both IL-12 and IL-23,²⁰ mirikizumab blocks only IL-23. It may therefore have different efficacy or safety. In a trial of patients with psoriasis, the anti-IL-23 antibody risankizumab was superior to ustekinumab.²¹ The anti-IL-23 antibodies appear to be safe. They do not have any black box warnings.

Dr Geert R. D'Haens and colleagues presented results from a phase 2 trial of mirikizumab as maintenance treatment.²² Results from the induction phase of the trial were presented at the 2018 Digestive Disease Week.²³ This trial is the first to evaluate an IL-23 antibody in ulcerative colitis. This analysis included 93 patients who responded to treatment and continued on the study. They were randomly assigned to 200 mg administered subcutaneously every 12 weeks or every 4 weeks. At week 52, between 37% and 46% of patients were in clinical remission. There were

no substantial differences in remission rates between biologic-naïve and biologic-experienced patients. The clinical response rate was even higher, at 70% to 80%. Endoscopic improvement ranged from 48% to 57%. Mirikizumab was well-tolerated, with few serious adverse events (3.2% overall). Based on the results of this trial, mirikizumab will be evaluated in a phase 3 development program. Potentially, IL-23 antibodies will provide another mechanism of action in the treatment armamentarium for IBD.

Disclosure

Dr Loftus has consulted for Eli Lilly, Janssen, Takeda, Pfizer, AbbVie, UCB, Amgen, Celltrion Healthcare, Celgene, Allergan, Bristol-Myers Squibb, Gilead, Boehringer Ingelheim, and Genentech. He has also received research support from Janssen, Takeda, Pfizer, AbbVie, UCB, Amgen, Genentech, Celgene, Gilead, MedImmune, Seres Therapeutics, and Roberts Clinical Trials.

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