GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

December 2019 Volume 15, Issue 12, Supplement 5

***A SPECIAL MEETING REVIEW EDITION***

# Highlights in IBD From the American College of Gastroenterology 2019 Annual Scientific Meeting and United European Gastroenterology Week 2019

A Review of Selected Presentations From the ACG 2019 Meeting • October 25-30, 2019 • San Antonio, Texas and UEG Week 2019 • October 19-23, 2019 • Barcelona, Spain

**Special Reporting on:**

- Early Clinical Response and Remission With Vedolizumab Versus Adalimumab in Ulcerative Colitis: Results From VARSITY
- Histologic Improvement With Vedolizumab Versus Adalimumab in Ulcerative Colitis: Results From VARSITY
- High Versus Standard Adalimumab Induction Dosing Regimens in Patients With Crohn's Disease or Ulcerative Colitis: Results From the SERENE-CD and SERENE-UC Induction Studies
- Transitioning From Vedolizumab IV to Vedolizumab SC in Patients With Ulcerative Colitis: Results From the VISIBLE Program
- Effects of Ustekinumab Maintenance Therapy on Endoscopic Improvement and Histologic Improvement in the UNIFI Phase 3 Study in Ulcerative Colitis
- Real-World Safety of Vedolizumab and Anti-TNF Therapies in Biologic-Naive Ulcerative Colitis and Crohn's Disease Patients: Results From the EVOLVE Study
- Clinical Effectiveness of First-Line Anti-TNF Therapies and Second-Line Anti-TNF Therapy Post–Vedolizumab Discontinuation in Patients With Ulcerative Colitis or Crohn's Disease
- Results From a Phase 2 Study of Risankizumab in Patients With Moderately to Severely Active Crohn's Disease
- U-ACHIEVE: A Phase 2 Study of Upadacitinib Induction in Patients With Moderate to Severe Ulcerative Colitis

**PLUS Meeting Abstract Summaries**

**With Expert Commentary by:**

**William J. Sandborn, MD**
Professor of Medicine
Chief, Division of Gastroenterology
Director, UCSD IBD Center
University of California San Diego
La Jolla, California

**ON THE WEB:**
**gastroenterologyandhepatology.net**

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

## 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**

**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-TNFα–experienced patients[2,3]

**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.

Entyvio vs HUMIRA®* (adalimumab)

THE FIRST HEAD-TO-HEAD STUDY of biologic therapies in UC[1,2]

NOW AVAILABLE in the *New England Journal of Medicine* or at Entyvio-VARSITY.com

*HUMIRA® AbbVie Inc. North Chicago, IL.

With... Entyvio® vedolizumab

GUT SELECTIVITY[4-9]

Entyvio helps address inflammation where it occurs—in the gut

Entyvio specifically binds to the α4β7 integrin and blocks the interaction between the α4β7 integrin and MAdCAM-1, which is mainly expressed on GI tract endothelial cells[3]

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[3,10]

## 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 ≥3% and ≥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.**

CD = Crohn's disease; GI = gastrointestinal; MAdCAM-1 = mucosal addressin cell adhesion molecule-1; TNF = tumor necrosis factor; UC = ulcerative colitis.

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

ENTYVIO is a trademark of Millennium Pharmaceuticals, Inc., registered with the U.S. Patent and Trademark Office and is used under license by Takeda Pharmaceuticals America, Inc.

©2019 Takeda Pharmaceuticals U.S.A., Inc. All rights reserved.
Printed in U.S.A./October 2019 MAT-USD-VED-19-00513

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

Takeda

**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**
**ENTYVIO (vedolizumab) for injection, for intravenous use**

## FULL PRESCRIBING INFORMATION

## 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 ≥3% of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥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 ≥3% of ENTYVIO-treated Patients and ≥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 ≥3 x 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).

Risk Summary

Available pharmacovigilance data, data from the ongoing pregnancy registry, and data from published case reports and cohort studies in pregnant women have not identified an ENTYVIO associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with inflammatory bowel disease in pregnancy *(see Clinical Considerations)*. 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 *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and miscarriage is 15 to 20%, respectively.

Clinical Considerations

*Disease-associated maternal and embryo/fetal risk*

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

*Fetal/Neonatal adverse reactions*

ENTYVIO administered during pregnancy could affect immune responses in the in utero exposed newborn and infant. The clinical significance of low levels of ENTYVIO in utero-exposed infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

*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).

### Lactation

Risk Summary

Available published literature suggests the presence of vedolizumab in human milk. The effects of local gastrointestinal exposure and expected low systemic exposure to vedolizumab on the breastfed infant are unknown. There are no data on the effects of vedolizumab on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENTYVIO and any potential adverse effects on the breastfed infant from ENTYVIO or from the underlying maternal condition.

### 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

Revised: May 2019

ENTYVIO is a trademark of Millennium Pharmaceuticals Inc. and is used under license by Takeda Pharmaceuticals America, Inc.

All other trademark names are the property of their respective owners.

©2014 – 2019 Takeda Pharmaceuticals America, Inc.

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

VMB245 R3_Brf. L-BZV-0519-8

# Early Clinical Response and Remission With Vedolizumab Versus Adalimumab in Ulcerative Colitis: Results From VARSITY

The double-blind, double-dummy phase 3b VARSITY trial (An Efficacy and Safety Study of Vedolizumab Intravenous [IV] Compared to Adalimumab Subcutaneous [SC] in Participants With Ulcerative Colitis) compared the efficacy and safety of vedolizumab vs adalimumab in patients with moderately to severely active ulcerative colitis.[1] The trial was conducted at 245 centers in 34 countries. Per the trial design, up to 25% of the patient population could have received previous treatment with a tumor necrosis factor (TNF) inhibitor other than adalimumab. Patients were randomly assigned to receive vedolizumab (300 mg intravenously on weeks 0, 2, and 6, and every 8 weeks thereafter) plus placebo injections or subcutaneous (SC) adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg every 2 weeks thereafter) plus infusions of placebo until week 50. The primary endpoint was clinical remission at week 52, defined as a total score of 2 or less on the Mayo scale and no subscore greater than 1. Other prespecified analyses included changes in fecal calprotectin levels, clinical response based on partial Mayo score, and the proportion of patients with a durable clinical remission at week 52. An analysis of early clinical response and clinical remission was presented at the American College of Gastroenterology (ACG) 2019 Annual Scientific Meeting.[2]

The trial included 383 patients in the vedolizumab arm and 386 patients in the adalimumab arm. Patient characteristics at baseline were generally well balanced between the 2 arms. The duration of ulcerative colitis was 7.3 ± 7.2 years in the vedolizumab arm vs 6.4 ± 6.0 years in the adalimumab arm. The rates of prior anti-TNF use were 20.8% vs 21.0%, respectively. A severe Mayo score was reported in 56.4% vs 54.4% of patients. The mean level of C-reactive protein was 10.6 ± 17.1 µg/mL vs 9.7 ± 16.7 µg/mL, and the mean fecal calprotectin concentration was 2929 ± 5920 µg/g vs 2771 ± 4064 µg/g.

Clinical response according to study visit based on change in partial Mayo score from baseline is shown in Figure 1. At week 14, a clinical response based on the complete Mayo score was reported in 67.1% of the vedolizumab arm vs 45.9% of the adalimumab arm (95% CI, 14.4-28.0; $P<.0001$). A clinical remission at week 14 was seen in 26.6% vs 21.2%, respectively (95% CI, –0.7 to 11.4; $P=.0824$).

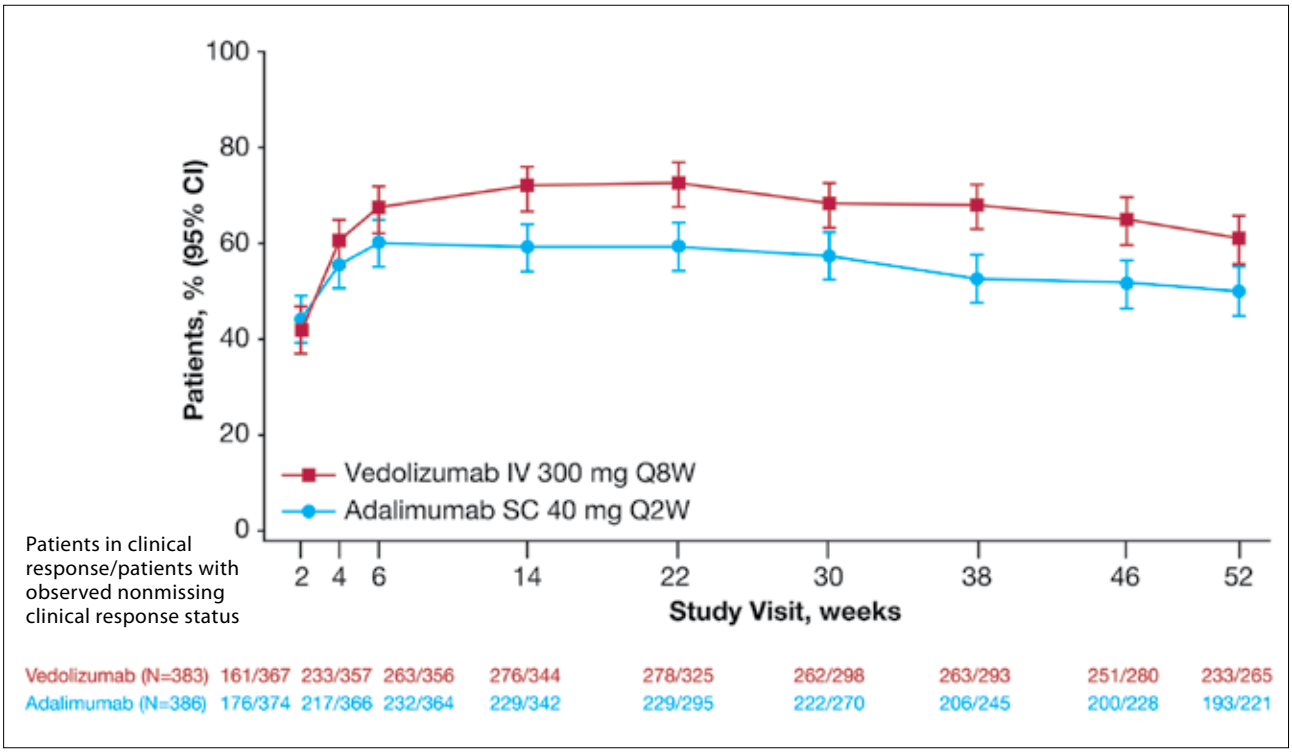


**Figure 1.** Clinical response by study visit based on change in partial Mayo score from baseline (full analysis set). IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous. Adapted from Danese S et al. ACG abstract P0524. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[2]

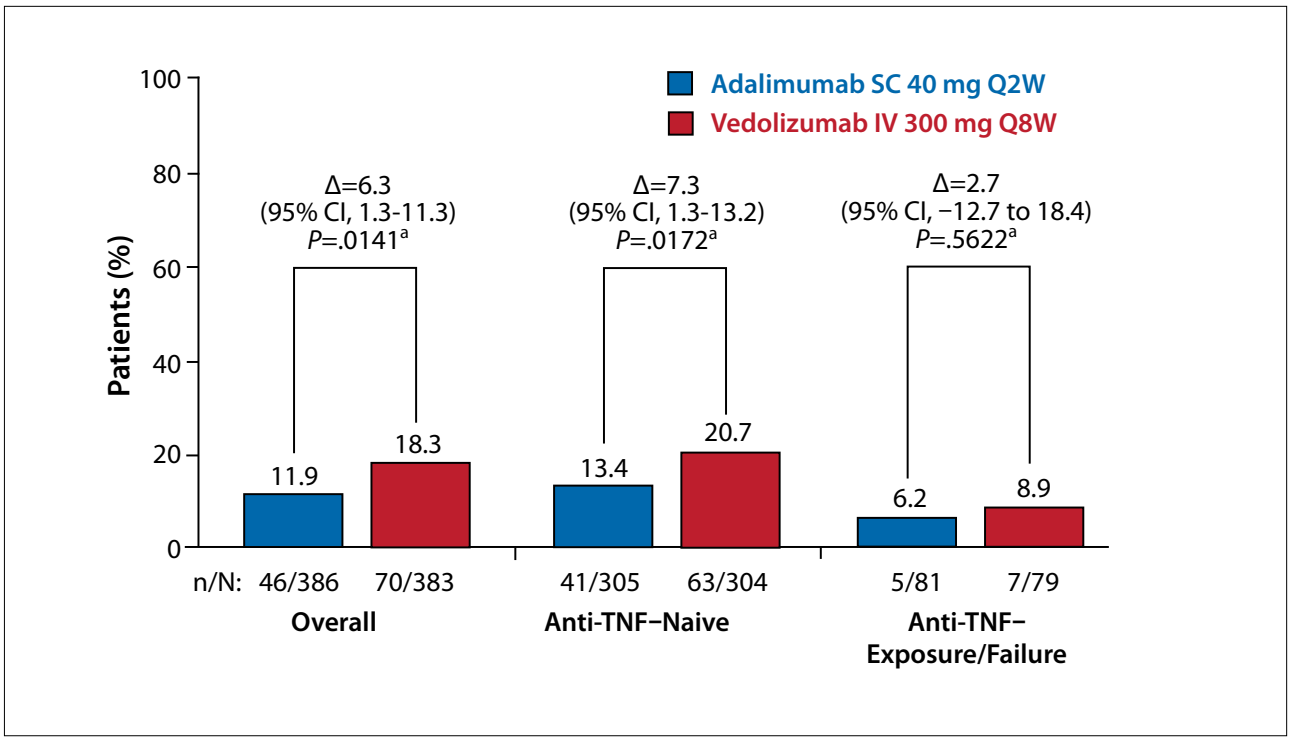


**Figure 2.** Durable clinical remission (full analysis set). IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNF, tumor necrosis factor. [a]Nominal *P*-value. Adapted from Danese S et al. ACG abstract P0524. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[2]

Among patients with prior exposure to an anti-TNF agent, the clinical remission rate at week 14 was 22.8% with vedolizumab vs 12.3% with adalimumab (95% CI, –1.5% to 22.2%; *P*=.0863). The proportion of patients with a durable clinical remission at week 52 was 18.3% in the vedolizumab arm vs 11.9% in the adalimumab arm (95% CI, 1.3%-11.3%; *P*=.0141; Figure 2). Among patients without prior exposure to an anti-TNF agent, the rate of durable remission was 20.7% vs 13.4%, respectively (95% CI, 1.3%-13.2%; *P*=.0172). From baseline to week 14, mean decreases in fecal calprotectin and C-reactive protein levels were higher with vedolizumab than adalimumab.

### ABSTRACT SUMMARY Oral ABX464 QD Is Safe and Efficacious During 52 Weeks Open-Label Maintenance Following a Placebo-Controlled Induction Study in Ulcerative Colitis Patients

ABX464 is an oral drug that upregulates the expression of microRNA-124, a key regulator of inflammation. ABX464-101 was a phase 2a trial that evaluated 8 weeks of daily ABX464 (50 mg) vs placebo as induction therapy in 32 patients with ulcerative colitis (UEG Week abstract LB06). After 8 weeks of therapy, microRNA-124 expression was significantly higher with ABX464 vs placebo (*P*=.004). Patients in the active treatment arm showed numerically superior rates of clinical remission (35% vs 11%; *P*=.16) and clinical response (70% vs 33%; *P*=.06), as well as a significantly improved rate of mucosal healing (50% vs 11%; *P*<.03). Twenty-two of these patients were enrolled in a 52-week maintenance study, during which they continued to receive ABX464 (50 mg daily). Nineteen patients (86%) completed 52 weeks of maintenance therapy and entered a second year of ABX464 treatment. Two patients left the study due to a lack of clinical efficacy, and 1 patient discontinued due to grade 2 headache. Endoscopies were performed in 16 patients (84%) at week 52 ± 3 months, and all of these patients had a Mayo endoscopic subscore of 0 or 1. The addition of rectal bleeding and stool frequency scores yielded a clinical remission rate of 75% at 52 weeks. In both the induction and maintenance studies, ABX464 showed good safety and tolerability.

## References

1. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med.* 2019;381(13):1215-1226.

2. Danese S, Loftus EV, Colombel JF, et al. Early clinical response and remission with vedolizumab versus adalimumab in ulcerative colitis: results from VARSITY [ACG abstract P0524]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

# Histologic Improvement With Vedolizumab Versus Adalimumab in Ulcerative Colitis: Results From VARSITY

In the VARSITY trial, vedolizumab was superior to adalimumab in achieving clinical remission (31.3% vs 22.5%; *P*=.0061) and endoscopic improvement (39.7% vs 27.7%; *P*=.0005) in patients with moderately to severely active ulcerative colitis.[1] A prespecified, exploratory endpoint analysis evaluated the rates of histologic remission and minimal histologic disease activity at weeks 14 and 52 in patients from the VARSITY study, and the results were presented at the ACG 2019 meeting.[2] Histologic remission was defined as a Geboes score of less than 2 or a Robarts Histopathology Index (RHI) score of less than 3. Minimal histologic disease was defined as a Geboes score of less than 3.2 or an RHI score of less than 5. In post hoc analyses, endoscopic improvement was defined as a Mayo score endoscopic subscore of 1 point or less.

The analysis included 769 patients who received at least 1 dose of study treatment: 383 in the vedolizumab arm and 386 in the adalimumab arm. The mean baseline disease activity was similar for both arms. The median duration of exposure was 477 days (range, 127-630 days) in the vedolizumab arm and 420 days (range, 71-454 days) in the adalimumab arm.

At week 14, rates of histologic remission based on the Geboes score were similar for both treatment arms in the overall study population (*P*=.1944), as well as in the subpopulations of patients without prior exposure to anti-TNF agents (*P*=.4348) and in patients with prior exposure/failure to an anti-TNF agent (*P*=.1180). When RHI scores were used, the rate of histologic remission was superior with vedolizumab in the overall study population (25.6% vs 16.1%; *P*=.0011), among patients without prior exposure to an anti-TNF agent (27.0% vs 19.0%; *P*=.0198), and among those with prior anti-TNF exposure/failure (20.3% vs 4.9%; *P*=.0038).

At week 52, based on the Geboes score, the proportion of patients with histologic remission was 10.4% in the vedolizumab arm vs 3.1% in the adalimumab arm (*P*<.0001). Among patients without prior exposure to an anti-TNF agent, the rates of histologic remission were 13.2% with vedolizumab vs 3.6% with adalimumab (*P*<.0001). In patients with prior exposure/failure to an anti-TNF agent, rates of histologic remission were similar in the treatment arms (*P*=1.0000). In the overall population, rates of histologic remission at week

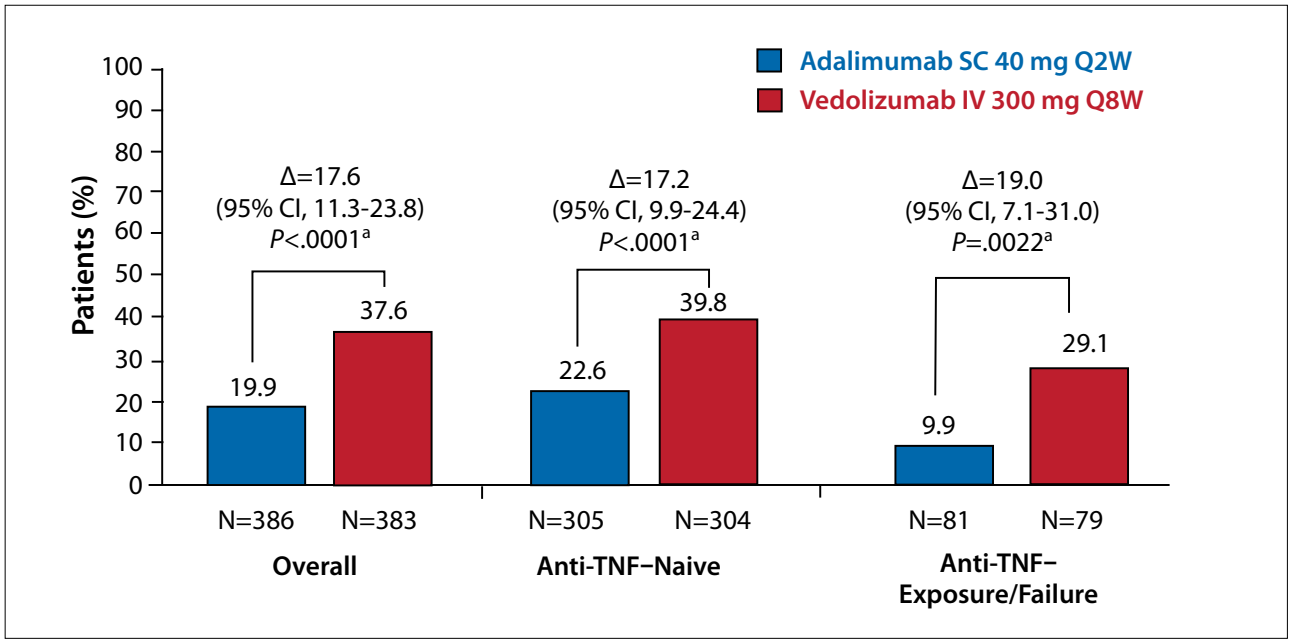


**Figure 3.** Histologic remission at week 52 (Robarts Histopathology Index score <3). IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNF, tumor necrosis factor. [a]Nominal *P*-value. Point estimates and 95% CIs were obtained using the Cochran-Mantel-Haenszel method with stratification by randomization stratification factor: concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF (Yes/No), or by the Fisher's exact method if the numerator was ≤5. Patients with missing endpoint data were considered treatment failures (ie, nonresponders). Adapted from Peyrin-Biroulet L et al. ACG abstract P1402. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[2]

**ABSTRACT SUMMARY Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Ulcerative Colitis: An Interim Analysis of an Open-Label, Long-Term Extension Study With Up to 5.5 Years of Treatment**

An OLE study of the OCTAVE Sustain and OCTAVE Induction trials included 944 patients who were treated for up to 5.5 years with tofacitinib (UEG Week abstract OP213). The dose of tofacitinib was 5 mg twice daily for 175 patients and 10 mg twice daily for 769 patients. No new safety signals emerged. An insufficient clinical response led 337 patients (35.7%) to discontinue treatment, and 78 patients (8.3%) discontinued due to AEs other than worsening ulcerative colitis. AEs of any grade were reported in 80.9% of patients, serious AEs in 17.2% of patients, and severe AEs in 11.5% of patients. At month 36, the rates of remission were 55.9% in the 5-mg arm vs 32.2% in the 10-mg arm. The rates of mucosal healing were 62.5% vs 35.8%, respectively, and the rates of clinical response were 65.8% vs 38.9%.

52 per the RHI score were 37.6% with vedolizumab vs 19.9% with adalimumab ($P$<.0001; Figure 3). These rates were 39.8% vs 22.6%, respectively ($P$<.0001), among patients who had not received a prior anti-TNF agent, and 29.1% vs 9.9% ($P$=.0022) among patients with prior exposure/failure to an anti-TNF agent. Vedolizumab was associated with superior rates of minimal histologic disease activity vs adalimumab at week 14 and at week 52 ($P$<.05 for each). The proportion of patients with histologic remission plus endoscopic improvement or minimal histologic disease activity plus endoscopic improvement at week 52 was superior with vedolizumab compared with adalimumab ($P$<.05).

## References

1. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381(13):1215-1226.
2. Peyrin-Biroulet L, Colombel JF, Loftus EV, et al. Histologic improvement with vedolizumab vs. adalimumab in ulcerative colitis: results from VARSITY [ACG abstract P1402]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

# High Versus Standard Adalimumab Induction Dosing Regimens in Patients With Crohn's Disease or Ulcerative Colitis: Results From the SERENE-CD and SERENE-UC Induction Studies

The SERENE-CD trial (Study to Evaluate Efficacy and Safety of Two Drug Regimens in Subjects With Moderate to Severe Crohn's Disease) and SERENE-UC trial (Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects With Moderate to Severe Ulcerative Colitis) evaluated adalimumab in a higher induction regimen (HIR) vs a standard induction regimen (SIR) in patients with Crohn's disease or ulcerative colitis. Results were presented at United European Gastroenterology (UEG) Week 2019.[1,2] These double-blind, multicenter studies enrolled patients with moderately to severely active disease. In both studies, patients were randomly assigned in a 3:2 manner to receive induction treatment with adalimumab HIR (160 mg on weeks 0, 1, 2, and 3) or adalimumab SIR (160 mg on week 0 and 80 mg on week 2). All patients then received adalimumab (40 mg) every other week from week 4 on.

The SERENE-CD study randomly assigned 308 patients to the HIR arm and 206 to the SIR arm. The induction regimen was completed by 92.9% vs 93.2%, respectively. Baseline characteristics were generally well balanced between the 2 arms. The median duration of Crohn's disease was 7.3 ± 8.5 years, 17.3% had prior exposure to infliximab, and 48.2% were receiving treatment with corticosteroids.

At week 4, the rates of clinical remission were 43.2% in the HIR arm and 43.7% in the SIR arm ($P$>.999). At week 12, rates of endoscopic response were 42.5% vs 39.3% ($P$=.509), respectively, and rates of endoscopic remission were 28.6% vs 26.2% ($P$=.694). The proportion of patients who discontinued corticosteroids during the study and achieved clinical remission at week 12 was 52.3% in the HIR arm vs 47.0% in the SIR arm, a difference that was not significant ($P$=.309). Significantly more patients in the HIR arm were in clinical remission at week 12 (62.3% vs 51.5%; $P$=.008) and had a clinical response at week 12 (83.4% vs 74.8%; $P$=.015). However, the ranked secondary endpoints did not reach statistical significance, based on prespecified testing requirements. A clear exposure-response relationship was observed for endoscopic response at week 12.

The SERENE-UC study randomly assigned 512 patients into the HIR arm and 340 into the SIR arm. Baseline characteristics were generally well balanced between the 2 arms. The mean duration of ulcerative colitis was 7.2 ± 7.1 years, 87.1% of patients had no prior exposure to a biologic

**Table.** Results for Secondary Efficacy Endpoints

| Endpoint at Week 8, n (%) | Adalimumab HIR (n=512) | Adalimumab SIR (n=340) | *P*-value |
|---|---|---|---|
| Endoscopic improvement[a] (endoscopic subscore of 0 or 1) | 159 (31.1) | 92 (27.1) | .182 |
| Fecal calprotectin <150 mg/kg | 115 (22.5) | 67 (19.8) | .283 |
| IBDQ response (increase of IBDQ ≥16 from baseline) | 342 (66.8) | 207 (60.9) | .063 |
| Clinical response per full Mayo score[a,b] | 241 (47.1) | 136 (40.0) | .034[c] |
| Endoscopic remission[a] (endoscopic subscore of 0) | 67 (13.1) | 34 (10.0) | .162 |

HIR, higher induction regimen; IBDQ, Inflammatory Bowel Disease Questionnaire; RBS, rectal bleeding score; SIR, standard induction regimen. [a]Endoscopy scored via a central reading protocol. [b]Clinical response per full Mayo score: decrease from baseline in the full Mayo score ≥3 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1. [c]Nominal *P*-value <.05. Adapted from Panés J et al. UEG Week abstract OP216. *United European Gastroenterol J*. 2019;7(8 suppl).[2]

agent, and 58.7% were receiving corticosteroids.

At week 8, the clinical remission rate was 13.3% for the HIR arm vs 10.9% in the SIR arm (*P*=.273). Similar outcomes were observed in both arms for endoscopic improvement (*P*=.182), fecal calprotectin level (*P*=.283), Inflammatory Bowel Disease Questionnaire response (*P*=.063), and endoscopic remission (*P*=.162; Table). The difference in clinical response based on the full Mayo score was nominally significant (*P*=.034), with a higher median score in the HIR patients. Trough levels of adalimumab were higher in the HIR arm vs the SIR arm at weeks 4 and 8. The adalimumab trough levels in the SIR arm were similar to those reported previously for the phase 3 ULTRA 2 study (Efficacy and Safety of Adalimumab in Subjects With Moderately to Severely Active Ulcerative Colitis).[3] Higher concentrations of adalimumab were associated with a higher rate of clinical remission; however, modeling indicated a more shallow exposure-response relationship than that observed in ULTRA 2. In conclusion, the HIR regimen did not demonstrate a benefit over the SIR regimen for patients with ulcerative colitis or Crohn's disease.

## References

1. D'Haens G, Sandborn WJ, Loftus EV, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active Crohn's disease: results from the SERENE-CD induction study [UEG Week abstract LB27]. *United European Gastroenterol J*. 2019;7(8 suppl).
2. Panés J, Colombel JF, D'Haens G, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active ulcerative colitis: results from the SERENE-UC induction study [UEG Week abstract OP216]. *United European Gastroenterol J*. 2019;7(8 suppl).
3. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-265.e1-e3.

# Transitioning From Vedolizumab IV to Vedolizumab SC in Patients With Ulcerative Colitis: Results From the VISIBLE Program

Vedolizumab is a monoclonal antibody directed at the $\alpha_4\beta_7$ integrin and is approved as an intravenous (IV) formulation (vedolizumab IV) to treat Crohn's disease and ulcerative colitis. The double-blind, placebo-controlled phase 3 VISIBLE 1 trial (Efficacy and Safety of Vedolizumab Subcutaneous [SC] as Maintenance Therapy in Crohn's Disease) investigated a SC formulation of vedolizumab (vedolizumab SC) as maintenance treatment in adults with moderately to severely active ulcerative colitis.[1] The study showed a significant increase in efficacy with vedolizumab SC vs placebo as maintenance therapy in patients with ulcerative colitis who had achieved a clinical response to induction therapy with vedolizumab IV.

A post hoc analysis, presented at the ACG 2019 meeting, evaluated the efficacy of vedolizumab among patients who transitioned from the IV dose to the SC dose in VISIBLE 1.[2] The analysis also included patients from the VISIBLE OLE (Open-Label Extension) study. The 383 enrolled patients initially received induction therapy with vedolizumab IV (300 mg on weeks 0 and 2). Patients with a clinical response at week 6 were randomly assigned 2:1:1 to receive maintenance treatment. One hundred six patients received vedolizumab SC (108 mg every 2 weeks) plus IV placebo (every 8 weeks). In the reference arm, 54 patients received vedolizumab IV (300 mg every 8 weeks) plus SC placebo (every 2 weeks). In the control arm, 56 patients received SC placebo every 2 weeks and IV placebo every 8 weeks. The primary endpoint of clinical remission was evaluated at week 52.

The analysis identified 106 patients who received 2 infusions of vedolizumab IV and then transi-

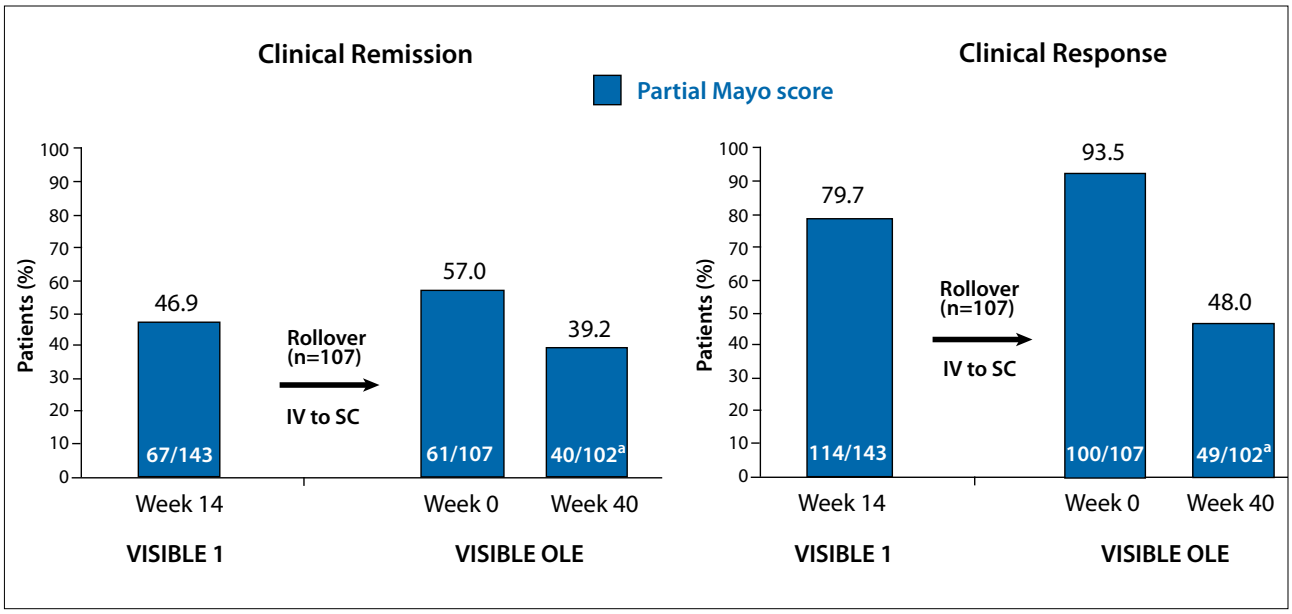


**Figure 4.** Vedolizumab clinical efficacy after transitioning to SC after 3 vedolizumab IV infusions. IV, intravenous; OLE, open-label extension; SC, subcutaneous. Clinical remission: complete Mayo score, or partial Mayo score, of ≤2 points and no individual subscore >1 point. Clinical response: complete Mayo score reduction of ≥3 points and ≥30% from baseline (week 0) (or partial Mayo score of ≥2 points and ≥25% from baseline) and accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. [a]102 patients were evaluable at week 40 of the OLE. Adapted from Wolf D et al. ACG abstract 3. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[2]

**ABSTRACT SUMMARY Early Histologic Improvement Demonstrated With Oral Ozanimod in Patients With Moderately to Severely Active Crohn's Disease in the STEPSTONE Trial**

The multicenter, single-arm phase 2 STEPSTONE trial (Efficacy and Safety Trial of RPC1063 for Moderate to Severe Crohn's Disease) evaluated ozanimod (1 mg/day) in patients with moderately to severely active Crohn's disease (UEG Week abstract OP148). At baseline, the 69 patients had a mean age of 38 years, a mean CDAI score of 321, and a mean RHI score of 16.3. The mean duration of Crohn's disease was 9 years since diagnosis. After 12 weeks of treatment, the mean change in the RHI score from baseline was –4.52 ± 9.48 points in the intention-to-treat population. In patients with prior biologic exposure, the mean change was –4.0 ± 8.59 points, vs –5.1 ± 10.75 points in patients without prior biologic exposure. Segment analysis revealed the greatest changes in RHI score in the rectum (–8.2 ± 10.59) and left colon (–8.1 ± 11.38).

tioned to vedolizumab SC. Among these patients, 23.6% had a clinical remission at week 6; the clinical remission rate increased to 46.2% by week 52. At week 6, 97.2% of these patients showed evidence of a clinical response. At week 52, the rate of clinical response was 65.1%. Among the 143 patients who initially received 3 vedolizumab IV infusions, the clinical remission rate was 46.9% at week 14 (Figure 4). One hundred seven of these patients transitioned to vedolizumab SC as part of VISIBLE OLE. The clinical remission rate was 57.0% at week 0 and 39.2% at week 40. At week 14 in VISIBLE 1, the clinical response rate among patients who had received 3 vedolizumab IV infusions was 79.7%. Among the 107 patients who rolled over to VISIBLE OLE, the clinical response rate was 93.5% at week 0 and 48.0% at week 40. Fifty-four patients transitioned to vedolizumab SC after receiving 8 infusions of vedolizumab IV. At week 52, the clinical remission rate in these patients was 42.6%. Among the 35 patients who continued to VISIBLE OLE, the clinical remission rate was 77.1% at week 0 and 76.9% at week 24. The clinical response rate at week 52 was 72.2%. In the VISIBLE OLE study, the clinical response rate was 100% at week 0 and 76.9% at week 24.

No new safety signals were observed. Among patients who received 2 vedolizumab IV infusions before transitioning to vedolizumab SC, 4.7% of patients experienced adverse events (AEs) leading to treatment discontinuation. Injection site reactions were observed in 10.4% of patients. Among patients who received

3 vedolizumab IV infusions prior to transitioning to vedolizumab SC, 4.7% of patients discontinued treatment due to an AE. Injection site reactions were observed in 1.9% of patients. In the group of patients who received 8 vedolizumab IV infusions before transitioning to vedolizumab SC, 2.6% discontinued study treatment due to an AE and 7.7% of patients developed an injection site reaction.

## References

1. Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis [published online August 28, 2019]. *Gastroenterology*. doi:10.1053/j.gastro.2019.08.027.
2. Wolf D, Danese S, Matthews B, et al. Transitioning from vedolizumab IV to vedolizumab SC in patients with ulcerative colitis: results from the VISIBLE program [ACG abstract 3]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

**ABSTRACT SUMMARY Vedolizumab Efficacy, Safety, and Pharmacokinetics With Reduced Frequency of Dosing From Every 4 to Every 8 Weeks in Patients With Ulcerative Colitis and Crohn's Disease**

To assess outcomes with reduced-intensity dosing, the GEMINI extended access program study evaluated vedolizumab at 300 mg administered intravenously every 8 weeks, for up to 56 weeks, in patients with IBD (UEG Week abstract OP217). The prospective, open-label, international, interventional study included patients who showed a clinical benefit from vedolizumab (300 mg every 4 weeks) during the GEMINI long-term safety study. Vedolizumab was administered in a reduced-intensity schedule to 88 patients with Crohn's disease and 79 patients with ulcerative colitis. At week 56, the reduced-frequency dosing was maintained in 86% of patients with Crohn's disease and 90% of those with ulcerative colitis. Rates of clinical remission and corticosteroid-free remission remained stable through week 56 in both patient groups. Patients who continued treatment with reduced-frequency dosing of vedolizumab showed consistently low levels of C-reactive protein. AEs related to vedolizumab were uncommon.

# Effects of Ustekinumab Maintenance Therapy on Endoscopic Improvement and Histologic Improvement in the UNIFI Phase 3 Study in Ulcerative Colitis

The phase 3 UNIFI trial (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis) compared the efficacy of ustekinumab vs placebo as maintenance therapy in 961 patients with moderate to severe ulcerative colitis. The study also evaluated the relationship between histologic improvement after induction treatment and outcomes during maintenance therapy, and results were presented at the ACG 2019 meeting.[1] Patients in the UNIFI induction study were randomly assigned into 3 arms: ustekinumab (~6 mg/kg), ustekinumab (130 mg), or placebo, all administered intravenously for 6 weeks. After induction therapy, patients with a clinical response by study week 16 were randomly assigned into 3 arms for the maintenance portion of the study: ustekinumab at 90 mg every 8 weeks, ustekinumab at 90 mg every 12 weeks, or placebo, all administered subcutaneously for up to 44 weeks. Biopsies of the distal colon were performed at screening and at maintenance weeks 0 and 44. The study defined histologic improvement as epithelial neutrophil infiltration in less than 5% of crypts; the absence of crypt destruction; and the absence of erosion, ulceration, or granulation of tissue. Endoscopic improvement was defined as a Mayo endoscopy score of 0 or 1. Histo-endoscopic mucosal healing referred to both histologic and endoscopic improvement.

In the placebo arm, the rates of histologic improvement, endoscopic improvement, and histo-endoscopic mucosal healing at week 44 were 32.9%, 28.6%, and 24.1%, respectively (Figure 5). Among patients who received ustekinumab at 90 mg every 12 weeks, the rates were 54.0% ($P$<.001), 43.6% ($P$=.002), and 38.8% ($P$=.002), respectively. Among patients who received ustekinumab at 90 mg every 8 weeks, the rates were 59.3% ($P$<.001), 51.1% ($P$<.001), and 45.9% ($P$<.001), respectively. At week 44, 344 patients had histologic improvement and 235 did not. Patients with histologic improvement had lower disease activity than those without, as assessed by several measurements: Mayo score (5.94 vs 1.88; $P$<.0001), partial Mayo score (3.56 vs 1.01; $P$<.0001), stool frequency score (1.49 vs 0.60; $P$<.0001), and rectal bleeding score (0.70 vs 0.04; $P$<.0001). Patients with histologic improvement at week 44 also exhibited greater disease improvement, based on changes in Mayo score (1.59 for those without improvement vs –1.57 for those with improvement; $P$<.0001), partial Mayo score (1.29 vs –0.75; $P$<.0001), stool frequency

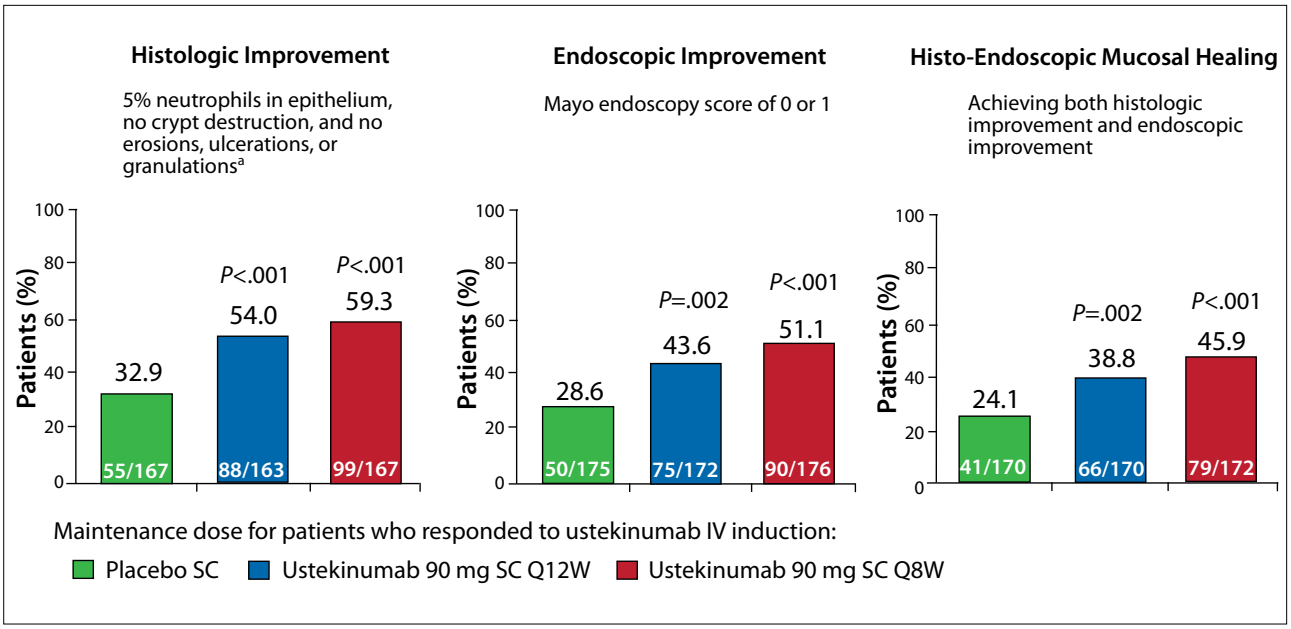


**Figure 5.** Histologic and endoscopic outcomes at maintenance week 44 in patients who responded to ustekinumab induction and were randomized to maintenance treatment. IV, intravenous; Q8W, every 8 weeks; Q12W, every 12 weeks; SC, subcutaneous. [a]Derived from features in Geboes score (Geboes K et al. *Gut*. 2000) that are correlated with endoscopic mucosal response (Li K et al. *JCC*. 2019). Adapted from Li K et al. ACG abstract 56. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[1]

score (0.40 vs –0.22; *P*<.0001), and rectal bleeding score (0.50 vs –0.10; *P*<.0001).

After induction therapy, 140 patients showed histologic improvement and 124 did not. Histologic improvement after induction was associated with positive outcomes at maintenance week 44, based on the proportion of patients with endoscopic improvement (47.0% for those without improvement vs 62.0% for those with improvement; *P*=.0135), histo-endoscopic mucosal healing (43.0% vs 59.0%; *P*=.0135), clinical remission (40.0% vs 54.0%; *P*=.0191), and corticosteroid-free clinical remission (39.0% vs 52.0%; *P*=.0354). Patients with histologic improvement after induction were more likely to demonstrate positive outcomes at weeks 8 and 44 compared with those who did not achieve histologic improvement after induction, including endoscopic improvement (31.0% vs 6.0%; *P*<.0001), histo-endoscopic mucosal healing (40.0% vs 0.0%; *P*<.0001), and clinical remission (26.0% vs 4.0%; *P*<.0001).

After completion of the induction regimen, 115 patients showed endoscopic improvement. Among these patients, 92 had concomitant evidence of histologic improvement and 23 did not. At week 44, patients with concomitant evidence of histologic improvement were significantly more likely to have a clinical response (84.0% vs 52.0%; *P*=.0038) than those without. Improvements in clinical remission (61.0% vs 39.0%; *P*=.0983) and corticosteroid-free clinical remission (58.0% vs 35.0%; *P*=.0628) did not reach statistical significance.

### ABSTRACT SUMMARY Long-Term Efficacy of Vedolizumab in Pediatric Inflammatory Bowel Disease

A retrospective study evaluated the efficacy of vedolizumab in pediatric patients (ACG abstract P1685). The analysis included 29 patients, whose median age was 14 ± 3.2 years. Most of the patients were male (59%), and most had Crohn's disease (55%). The median duration of treatment with vedolizumab was 21.3 months (interquartile ratio, 13.8-39.1 months). Vedolizumab was discontinued in 5 patients for primary nonresponse and in 5 patients for secondary nonresponse. After 1 year of vedolizumab treatment, clinical remission was observed in 8 of 13 patients with Crohn's disease (62%) and in 5 of 11 patients with ulcerative colitis (45%). At 2 years, sustained clinical remission was observed in 8 of 9 patients (89%) vs 3 of 5 patients (60%), respectively. Headache and fatigue were the most common AEs. None of the patients discontinued vedolizumab due to an AE.

## Reference

1. Li K, Friedman JR, Marano C, et al. Effects of ustekinumab maintenance therapy on endoscopic improvement and histologic improvement in the UNIFI phase 3 study in ulcerative colitis [ACG abstract 56]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

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

The GEMINI trials investigated the efficacy and safety of vedolizumab induction and maintenance therapy in patients with moderately to severely active inflammatory bowel disease (IBD).[1,2] The trials demonstrated a favorable safety profile for vedolizumab compared with anti-TNF agents in IBD patients. The EVOLVE study (ENTYVIO Outcomes in Real-World Biologic-Naïve Ulcerative Colitis and Crohn's Disease Patients) investigated long-term outcomes from vedolizumab vs anti-TNF agents in a retrospective chart review presented at the ACG 2019 meeting.[3] The international, noninterventional study evaluated treatment efficacy, treatment patterns, health care resource use, and safety for up to 24 months among patients with ulcerative colitis or Crohn's disease who had no prior exposure to biologic agents. Anti-TNF agents included adalimumab, infliximab, golimumab, and certolizumab pegol. The study enrolled patients with at least 6 months of follow-up data.

Among the 604 patients with ulcerative colitis, treatments included vedolizumab in 380 and anti-TNF therapy in 224. Among the 491 patients with Crohn's disease, treatments consisted of vedolizumab in 218 and anti-TNF therapy in 273. At baseline, patients treated with vedolizumab were older than those treated with anti-TNF agents, for both the ulcerative colitis (45.7 vs 39.6 years; $P<.01$) and the Crohn's disease (51.7 vs 39.7 years; $P<.01$) cohorts. The ulcerative colitis cohort had significantly more men in the vedolizumab group (59.5% vs 48.7%; $P=.01$). The median disease duration was longer for patients who received vedolizumab in both the ulcerative colitis and Crohn's disease cohorts ($P<.01$). The median follow-up was 15.3 months (range, 3.0-47.0 months) for the vedolizumab cohort and 16.3 months (range, 3.5-51.0 months) for the anti-TNF cohort.

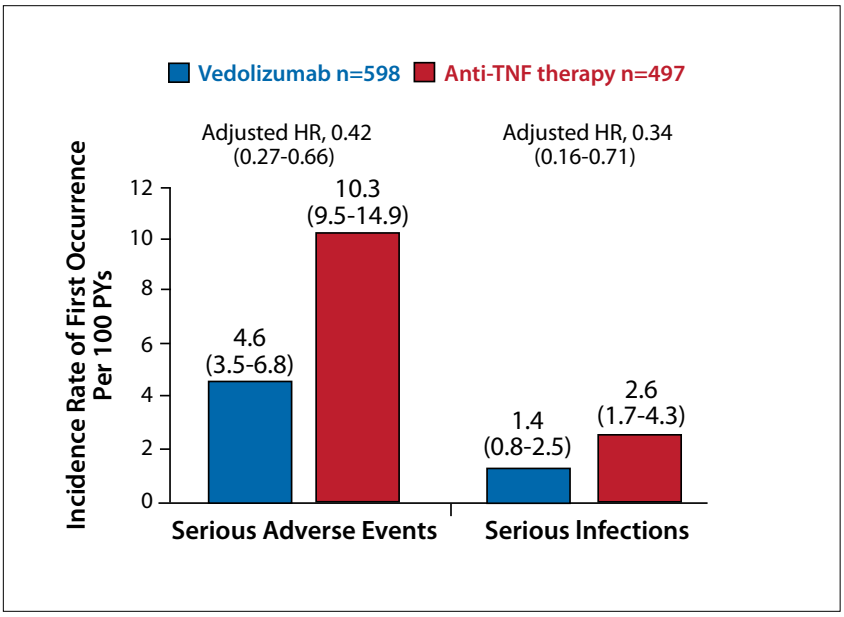


**Figure 6.** Serious adverse events and serious infections following vedolizumab and anti-TNF therapies in the UC and CD population. Incidence and 95% CIs are shown above each bar. HRs show the point estimate and 95% CIs. Half-lives for treatment: vedolizumab: 125 days (18 weeks), infliximab (and biosimilars): 47.5 days (6.8 weeks), adalimumab (and biosimilars): 70 days (10 weeks), golimumab: 70 days (10 weeks), certolizumab pegol: 70 days (10 weeks). CD, Crohn's disease; HR, hazard ratio; PY, patient year; TNF, tumor necrosis factor; UC, ulcerative colitis. Adapted from Yarur A et al. ACG abstract P2280. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[3]

The rates of serious AEs were 8.2% for the vedolizumab group vs 19.2% for the anti-TNF group among patients with ulcerative colitis. These rates were 12.4% vs 19.1% among patients with Crohn's disease. Across the entire study population, the rate of serious AEs was 4.6% with vedolizumab vs 10.3% with anti-TNF agents (adjusted hazard ratio [HR], 0.42; 95% CI, 0.27-0.66; Figure 6). The rate of serious infections was 1.4% vs 2.6%, respectively (adjusted HR, 0.34; 95% CI, 0.16-0.71). Among ulcerative colitis patients, the rate of serious AEs was 3.8% with vedolizumab vs 11.3% with anti-TNF agents (adjusted HR, 0.34; 95% CI, 0.19-0.63). The rate of serious infections was 1.4% vs 2.1%, respectively (adjusted HR, 0.30; 95% CI, 0.09-0.94). For Crohn's disease patients, the rate of serious AEs was 3.0% with vedolizumab vs 5.7% with anti-TNF agents (adjusted HR, 0.47; 95% CI, 0.22-1.02). The rate of serious infections was 1.5% vs 3.0% (adjusted HR, 0.20; 95% CI, 0.06-0.62).

## References

1. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol.* 2017;15(2):229-239.e5.

2. Sands BE, Sandborn WJ, Van Assche G, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease in patients naive to or who have failed tumor necrosis factor antagonist therapy. *Inflamm Bowel Dis*. 2017;23(1):97-106.
3. Yarur A, Mantzaris GJ, Kopylov U, et al. Real world safety of vedolizumab and anti-TNF therapies in biologic-naïve ulcerative colitis and Crohn's disease patients: results from the EVOLVE study [ACG abstract P2280]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

# Clinical Effectiveness of First-Line Anti-TNF Therapies and Second-Line Anti-TNF Therapy Post–Vedolizumab Discontinuation in Patients With Ulcerative Colitis or Crohn's Disease

A retrospective study presented at the ACG 2019 meeting evaluated the long-term efficacy of anti-TNF treatment administered as first-line therapy or as second-line therapy—after treatment with vedolizumab—in patients with IBD.[1] The study included patients from Canada, the United States, and Greece. Medical chart data were abstracted across 37 sites for patients who initiated treatment with vedolizumab or an anti-TNF agent between May 2014 and June 2017. Clinical efficacy data were collected from the initiation of first- or second-line treatment until death or the date of chart abstraction. Cumulative rates of treatment persistence, clinical response, and clinical remission were estimated over 6 months according to disease state (ulcerative colitis or Crohn's disease), as well as for the combined IBD population.

Among 497 patients who received first-line anti-TNF therapy, 224 had ulcerative colitis and 273 had Crohn's disease. Among 82 patients who received second-line anti-TNF therapy, 58 had ulcerative colitis and

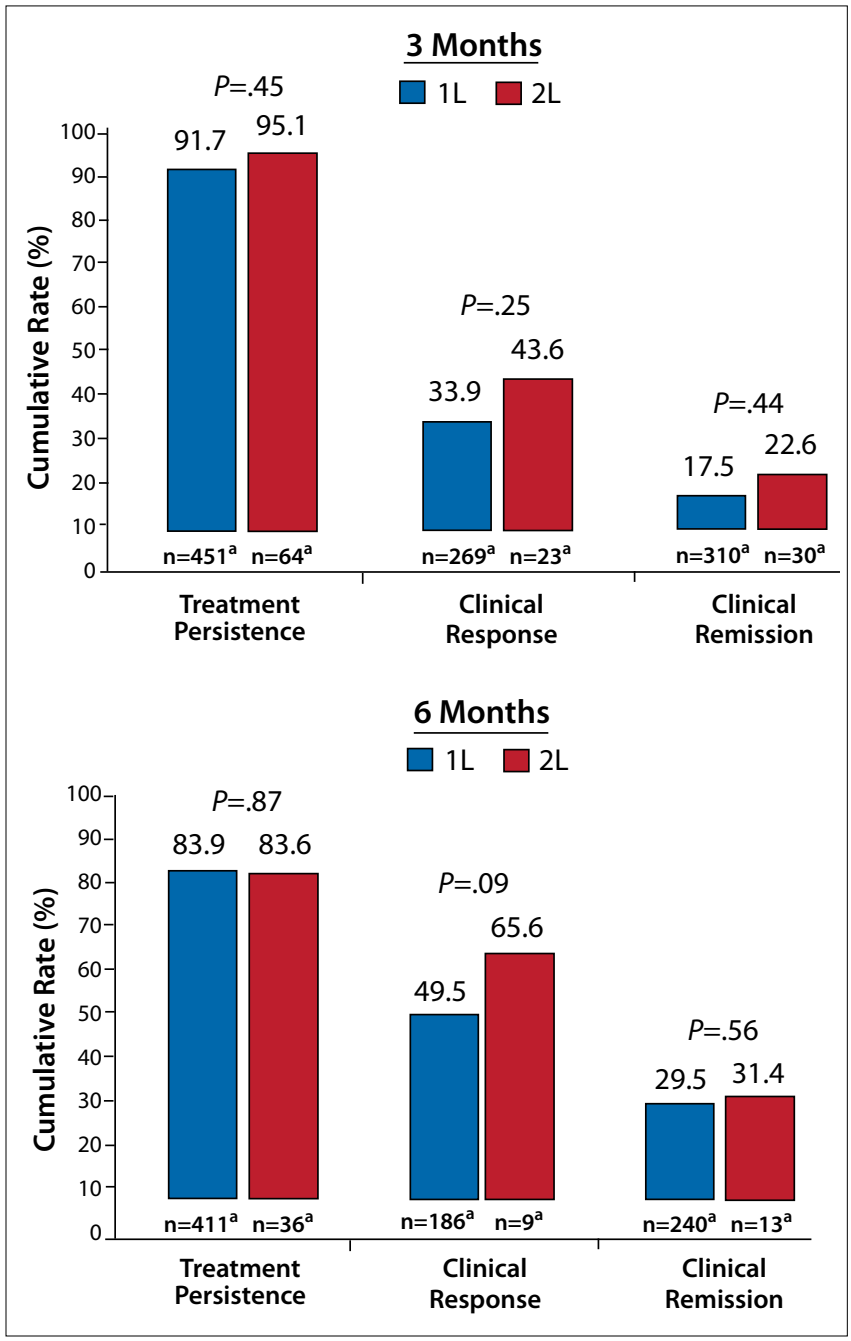


**Figure 7.** 2L[b] anti-TNF effectiveness in UC and CD. CD, Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis; 1L, first-line; 2L, second-line. [a]n at risk. [b]Anti-TNF used as a 2L therapy (after exposure to vedolizumab as a 1L therapy) vs anti-TNF used as a 1L therapy. Adapted from Bressler B et al. ACG abstract 40. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[1]

24 had Crohn's disease. In the cohort of patients who received an anti-TNF agent as first-line therapy, 53% received infliximab, 41% received adalimumab, 5% received golimumab, and 1% received certolizumab pegol. In the cohort of patients who received an anti-TNF agent as first-line therapy, 79% received infliximab, 20% received adalimumab, and 1% received golimumab. The cohort of patients who received first-line anti-TNF therapy had a mean age of 39.6 ± 15.2 years, and the median disease duration was 2.0 years (range, 0.01-49.0 years). Disease severity was moderate in 43.5% and severe in 29.3% of patients. The cohort of patients who received second-line anti-TNF therapy after having received first-line vedolizumab had a mean age of 49.4 ± 18.6 years, and a median disease duration of 3.7 years (range, 0.05-54.0 years). Disease severity was moderate in 56.5% and severe in 15.9% of patients. Prior IBD-related surgeries were reported in 3.4% of patients who received anti-TNF therapy as first-line treatment vs 1.2% of those who received it as second-line therapy. IBD required hospitalization in the prior 12 months in 15.1% vs 8.5% of patients.

Data collected after 3 or 6 months of therapy generally showed similar efficacy whether the anti-TNF agent was administered as first-line or second-line treatment. At 6 months, among patients with ulcerative colitis, rates of treatment persistence were 76.6% for the first-line cohort vs 79.5% for the second-line cohort (*P*=.50). Rates of clinical response were 57.1% vs 61.1% (*P*=.58), respectively, and rates of clinical remission were 19.6% vs 14.7% (*P*=.69). Among patients with Crohn's disease, rates of treatment persistence at 6 months were 90.0% in the first-line cohort vs 92.2% in the second-line cohort (*P*=.82). Rates of clinical response were 43.5% vs 74.8% (*P*=.13). The rate of clinical remission was significantly higher with second-line treatment (36.2% vs 74.6%); however, only 1 patient was at risk in the second-line cohort.

An analysis of the combined ulcerative colitis and Crohn's disease population showed that second-line anti-TNF therapy after vedolizumab yielded similar efficacy outcomes compared with first-line anti-TNF therapy. At 6 months, rates of treatment persistence were 83.9% in the first-line cohort vs 83.6% in the second-line cohort (*P*=.87; Figure 7). Rates of clinical response were 49.5% vs 65.6% (*P*=.09), respectively, and rates of clinical remission were 29.5% vs 31.4% (*P*=.56). The study authors noted that a limitation to the analysis was that the second-line cohort included only 82 patients, rendering it impossible to stratify outcomes based on reason for discontinuation of first-line vedolizumab.

In summary, cumulative rates of treatment persistence, clinical response, and clinical remission were similar for patients who received anti-TNF therapy as either first-line treatment or second-line treatment after vedolizumab. The results support the use of vedolizumab as a first-line agent for the treatment of patients with moderately to severely active ulcerative colitis or Crohn's disease.

## Reference

1. Bressler B, Yarur A, Kopylov U, et al. Clinical effectiveness of first-line anti-TNF therapies and second-line anti-TNF therapy post-vedolizumab discontinuation in patients with ulcerative colitis or Crohn's disease [ACG abstract 40]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

# Results From a Phase 2 Study of Risankizumab in Patients With Moderately to Severely Active Crohn's Disease

Risankizumab is a humanized antibody that inhibits interleukin-23 activity by binding to the p19 subunit. A phase 2 study evaluated the safety and efficacy of risankizumab in patients with moderate to severe Crohn's disease.[1] Eligible patients had had Crohn's disease for at least 3 months. Moderate to severe disease was defined by a Crohn's Disease Activity Index (CDAI) score of 220 to 450, with mucosal ulcers in the ileum and/or colon, and a Crohn's Disease Endoscopic Index of Severity (CDEIS) score of at least 7 as assessed by a central reader who was blind to the treatment groups. Patients with isolated ileitis had a CDEIS score of at least 4.

After stratification for prior exposure to an anti-TNF agent, 121 patients were randomly assigned into 3 arms: risankizumab at 600 mg, risankizumab at 200 mg, or placebo, all administered intravenously at weeks 0, 4, and 8. At week 12, the clinical remission rate was 31% for the pooled risankizumab arms vs 15% for the placebo arm (95% CI, 0.1-30.1; *P*=.0489). The most common AE was nausea, and the most common serious AE was worsening of Crohn's disease.

Data from the induction phase were analyzed to evaluate early symptom improvement during the trial and were presented at the ACG 2019 meeting.[2] Baseline characteristics were similar among the 3 arms. The mean disease duration was 13.4 ± 9.4 years, and 94.2% of patients had received prior anti-TNF therapy.

Compared with placebo, the 600-mg dose of risankizumab significantly reduced the median CDAI score and the median abdominal pain score at

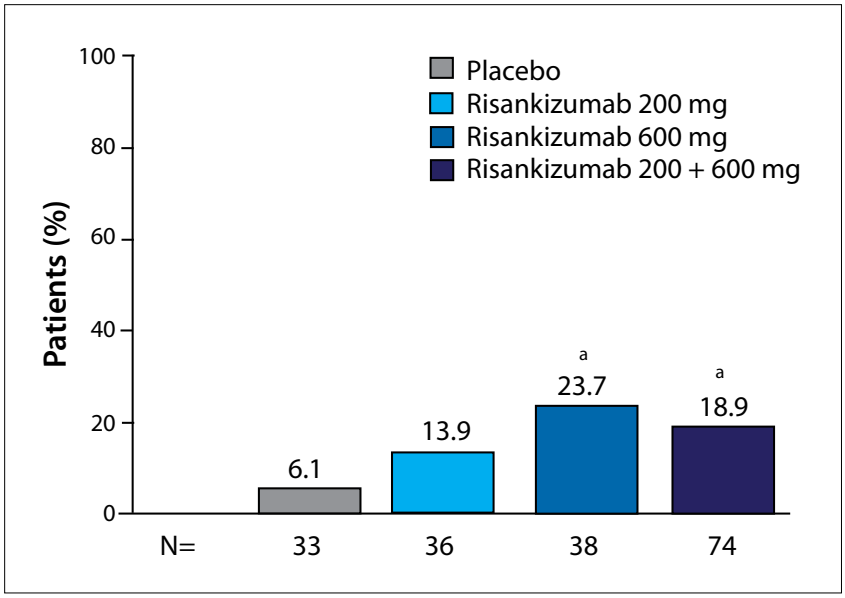


**Figure 8.** Clinical remission based on symptom improvement (SF ≤2.8 and AP ≤1, both not worse than baseline) at week 12. NRI analysis. AP, abdominal pain; NRI, nonresponder imputation; SF, stool frequency. [a]*P*<.05 for risankizumab vs placebo. Adapted from Feagan BG et al. ACG abstract P2319. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[2]

week 2 (*P*<.001) and at all time points through week 12 (*P*<.05). Significant improvements in average daily stool frequency were observed for the pooled risankizumab arms compared with placebo at all time points (*P*<.05). The median change in abdominal pain score from baseline was significantly improved for the pooled risankizumab arms vs placebo at each time point through week 12 (*P*<.05). Based on symptom improvement, the 600-mg risankizumab cohort had a significantly higher rate of clinical remission vs placebo (23.7% vs 6.1%; *P*<.05; Figure 8).

A 3-year interim analysis of the OLE study of the same phase 2 trial, also presented at the ACG 2019 meeting, included 65 adults with Crohn's disease.[3] The median duration of disease was 10 years (range, 2-38 years). Patients in the OLE study received maintenance risankizumab at 180 mg subcutaneously every 8 weeks. The mean exposure to risankizumab was 866.8 ± 316.6 days, and 27.7% of patients had discontinued from the study. At week 0 of the OLE study, 72% of patients were in clinical remission, and 43% had endoscopic remission. Efficacy endpoints were sustained through week 104, with 85.4% of patients in clinical remission and 63.6% of patients in endoscopic remission, based on an observed case analysis. No new safety signals emerged.

## References

1. Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2017;389(10080):1699-1709.
2. Feagan BG, Sandborn WJ, D'Haens GR, et al. Early symptom improvement with risankizumab treatment in patients with moderately to severely active Crohn's disease: analysis from a phase 2 study [ACG abstract P2319]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
3. Ferrante M, Feagan BG, Panés J, et al. Long-term safety and efficacy of risankizumab treatment in patients with Crohn's disease: 3-year interim results from the ongoing phase 2 open-label extension study [ACG abstract P2291]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

# U-ACHIEVE: A Phase 2 Study of Upadacitinib Induction in Patients With Moderate to Severe Ulcerative Colitis

Upadacitinib is an oral, selective inhibitor of Janus kinase 1. The phase 2b U-ACHIEVE study evaluated the efficacy and safety of upadacitinib induction therapy in patients with severe or refractory ulcerative colitis.[1-3] The 8-week, double-blind, placebo-controlled, dose-ranging study enrolled patients with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to biologic or immunosuppressive therapies or to corticosteroids. Eligible patients had an adapted Mayo score of 5 to 9 points and a centrally read endoscopy score of 2 to 3. After stratification, patients were randomly assigned to receive 8 weeks of placebo or extended-release upadacitinib at a daily dose of 7.5 mg, 15 mg, 30 mg, or 45 mg. The 250 patients had a mean age of 42.3 ± 14.2 years, and a mean disease duration of 8.2 ± 2.5 years. At week 8, a dose-response relationship was observed for all efficacy endpoints, including endoscopic outcomes, histologic outcomes, and mucosal healing. All efficacy endpoints were significantly improved with upadacitinib at the 2 higher dose levels compared with placebo (*P*<.05).

Part 2 of the U-ACHIEVE study

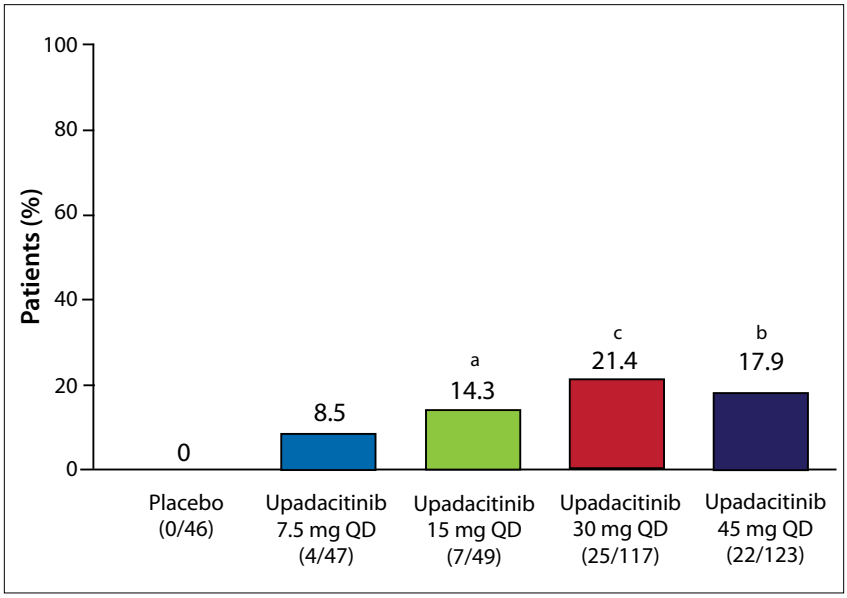


**Figure 9.** Clinical remission per adapted Mayo score at week 8. QD, once daily. [a]*P*<.05; [b]*P*<.01; [c]*P*<.001, for upadacitinib vs placebo. Adapted from Higgins P et al. ACG abstract P1935. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.[2]

### ABSTRACT SUMMARY The Vedolizumab Pregnancy Exposure Registry: An OTIS Pregnancy Study Update

A study conducted by the Organization of Teratology Information Specialists is investigating outcomes in pregnant women treated with vedolizumab for ulcerative colitis or Crohn's disease (ACG abstract P0525). Data were collected from the Vedolizumab Pregnancy Exposure Registry in the United States and Canada. Outcome data were available for 223 women, including 53 who had been treated with vedolizumab for at least part of their first trimester, 88 in the disease-matched group, and 82 in the healthy control group. The proportion of pregnancies that ended with a live-born infant was 94.3% in the vedolizumab-exposed group, 95.5% in the disease-matched group, and 91.5% in the healthy control group. No major structural birth defects were reported for the vedolizumab-treated group, compared with 5.7% in the disease-matched group and 5.3% in the healthy control group. The study is ongoing.

enrolled an additional 132 patients to treatment with 30 mg/day or 45 mg/day of upadacitinib, and the combined results were presented at the ACG 2019 meeting.[2] The overall population of 382 patients had a mean age of 42.7 ± 14.3 years, and a mean disease duration of 8.4 ± 7.4 years. The trial achieved its primary endpoint of clinical remission at week 8 based on the adapted Mayo score. These rates were 0% in the placebo arm vs 14.3% in the 15-mg upadacitinib arm (*P*<.05), 21.4% in the 30-mg arm (*P*<.001), and 17.9% in the 45-mg arm (*P*<.01; Figure 9). A significant improvement with upadacitinib at the 2 higher dose levels vs placebo was seen at 2- and 8-week assessments of all other endpoints, including endoscopic improvement or remission, clinical response, and histologic improvement. The rates of AEs were similar across the 4 upadacitinib doses and were numerically higher in the placebo arm.

A separate analysis, also presented at the ACG 2019 meeting, evaluated the efficacy of upadacitinib induction treatment in 142 patients who, at baseline, had an inadequate response to 2 or more biologic therapies, had pancolitis, or had an adapted Mayo score higher than 7.[1] For the cohorts of patients who had been treated with 2 or more biologic agents or who had pancolitis, upadacitinib doses of 30 mg or 45 mg yielded significantly higher rates of endoscopic improvement, clinical response based on adapted Mayo score, and clinical response based on the partial Mayo score compared with placebo (nominal *P*<.05).

## References

1. D'Haens G, Lindsay JO, Loftus EV, et al. Efficacy of upadacitinib as an induction therapy in severe and refractory ulcerative colitis: sub-group analysis of the phase 2b study U-ACHIEVE [ACG abstract P0486]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

2. Higgins P, Hébuterne X, Siffledeen J, et al. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: combined results from 382 subjects in the phase 2b study U-ACHIEVE [ACG abstract P1935]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

3. Sandborn WJ, Schreiber S, Lee SD, et al. 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 [ECCO abstract OP14]. *J Crohns Colitis*. 2019;13(suppl 1).

# Highlights in IBD From the American College of Gastroenterology 2019 Annual Scientific Meeting and United European Gastroenterology Week 2019: Commentary

William J. Sandborn, MD
Professor of Medicine
Chief, Division of Gastroenterology
Director, UCSD IBD Center
University of California San Diego
La Jolla, California

This year's American College of Gastroenterology (ACG) Annual Scientific Meeting and United European Gastroenterology (UEG) Week featured a number of important oral and poster presentations on the management of inflammatory bowel disease (IBD). New data on efficacy, real-world effectiveness, safety, and other issues were presented on various treatment options, including vedolizumab, adalimumab, ustekinumab, and tofacitinib.

## Vedolizumab

In the VARSITY study (An Efficacy and Safety Study of Vedolizumab Intravenous [IV] Compared to Adalimumab Subcutaneous [SC] in Participants With Ulcerative Colitis), 769 patients with ulcerative colitis were randomized to a year of therapy with either adalimumab at the US Food and Drug Administration (FDA)-approved dose or vedolizumab at the FDA-approved dose, and were compared over time.[1] The primary endpoint was remission at week 52, although there were a variety of other endpoints of interest. The ACG 2019 meeting featured 2 analyses of this trial. One of the analyses, conducted by Dr Silvio Danese and colleagues, focused on early clinical response and remission.[2] There has long been the notion that anti–tumor necrosis factor (TNF) agents work faster than anti-integrin agents, so this head-to-head comparison was an opportunity to find out if that idea is actually true. By 14 weeks of therapy, essentially at the induction endpoint, the results for each arm were almost the same, with vedolizumab actually having numerically higher rates of clinical response and remission, although the differences were not significant. However, over the course of a year, those differences became significant, and the trend favoring vedolizumab could be seen as early as 6 weeks. This shows that the idea that vedolizumab (and anti-integrin therapy) is slower-acting than anti-TNF therapy is not correct, and that both of these classes of drugs can work fairly quickly in a number of patients.

The other analysis of the VARSITY trial focused on histology. Patients underwent a flexible sigmoidoscopy or colonoscopy at baseline, an end-of-induction evaluation at week 14, and another evaluation at week 52. Dr Laurent Peyrin-Biroulet and colleagues found that vedolizumab had higher rates of histologic remission and minimal residual histologic disease activity at both weeks 14 and 52.[3] This adds to the trial's primary outcome of clinical remission, showing that histologic remission can also be obtained in patients over time. Once again, the difference was significant at week 52 and trended toward favoring vedolizumab earlier, at week 14.

Findings from 2 studies on the real-world effectiveness of vedolizumab were also presented at the ACG 2019 meeting. In a large multicenter retrospective study, Dr Brian Bressler and colleagues looked at the effectiveness of anti-TNF therapy in the real world when used second line after failing first-line biologic therapy with vedolizumab.[4] In the clinical trials of vedolizumab, the converse was examined; some patients were naive to biologics and others had previously received anti-TNF therapy and failed it.[5,6] In general, the benefit was less robust in patients who had failed anti-TNF therapy. The study conducted by Dr Bressler and colleagues, which included both Crohn's disease patients and ulcerative colitis patients, found that the results were fairly similar whether patients received first-line biologic therapy with an anti-TNF agent or whether patients received first-line therapy with vedolizumab, failed it, and then received second-line therapy with an anti-TNF agent.[4] In the clinical trials of vedolizumab, there had been a sense that patients do not do as well with vedolizumab if they failed anti-TNF therapy; however, this observational study suggests that if patients start with vedolizumab and fail it, anti-TNF therapy works about as well as it does if patients start with it. That is an interesting finding. It is

generally thought that vedolizumab is a safer therapy than anti-TNF therapy, so with the finding from this study, a reasonable treatment approach could be to start with vedolizumab and see if it works. If it does, the patient has received the benefits of the favorable safety profile of vedolizumab. However, if vedolizumab does not work, no harm has really been done in terms of then going to an anti-TNF therapy second, rather than having gone to it first.

In the other study, Dr Andres Yarur and colleagues looked at safety in the real world in patients on anti-TNF therapy vs vedolizumab therapy.[7] Among anti-TNF–naive patients, vedolizumab tended to have a better safety profile, whereas in anti-TNF–failure patients, that benefit was less apparent. This fits in with the idea that doctors might try vedolizumab first because of its safety profile and that they would see a benefit in those naive patients, but that if vedolizumab does not work, they can always go to anti-TNF therapy.

The ACG 2019 meeting also included findings from a trial by the Organization of Teratology Information Specialists on vedolizumab pregnancy exposure. Dr Christina Chambers and colleagues identified outcomes for pregnancy in 223 women, 53 of whom received vedolizumab.[8] The researchers found that there were no major structural birth defects reported in the vedolizumab group, compared to 5.7% and 5.3% in the disease-matched group and healthy control group, respectively. Thus, there seemed to be no signal for an increased malformation risk in patients who were undergoing treatment with vedolizumab and became pregnant.

Another study from this meeting looked at vedolizumab in the pediatric IBD population. Dr Harry E. Sarles and colleagues conducted a retrospective study of 29 pediatric patients who had received vedolizumab off-label (all had previously been treated with anti-TNF agents).[9] Patients had either ulcerative colitis (n=13) or Crohn's disease (n=16). The researchers found that vedolizumab was effective for achieving clinical remission in both ulcerative colitis and Crohn's disease in pediatric patients who had a history of anti-TNF failure, and the drug was generally well tolerated. These are promising preliminary data that a drug approved for adult ulcerative colitis and Crohn's disease may also be useful in children.

## Adalimumab

The SERENE trials are a set of head-to-head trials, one for ulcerative colitis and one for Crohn's disease, comparing standard-dose adalimumab to a more intensive induction regimen of adalimumab. At UEG Week 2019, I presented findings from the SERENE-UC trial (Study to Evaluate the Safety and Efficacy of Two Drug Regimens in Subjects With Moderate to Severe Ulcerative Colitis).[10] Patients with moderate to severe ulcerative colitis (n=852) were randomized to standard-dose adalimumab (160 mg at week 0, 80 mg at week 2, and then 40 mg at weeks 4 and 6) or high-dose adalimumab (160 mg weekly at weeks 0, 1, 2, and 3, and then 40 mg at weeks 4 and 6). Patients were assessed at week 8 for efficacy. Approximately 13% of the patients had previously received anti-TNF therapy, and, conversely, approximately 87% of patients were naive to biologic therapy. We found that there was no significant difference in the rates of clinical remission, clinical response, and endoscopic improvement between standard-dose and high-dose adalimumab.

In the SERENE-CD trial (Study to Evaluate Efficacy and Safety of Two Drug Regimens in Subjects With Moderate to Severe Crohn's Disease), presented by Dr Geert D'Haens at UEG Week 2019, 514 Crohn's disease patients were randomized to standard-dose adalimumab (160 mg at week 0, 80 mg at week 2, and 40 mg every other week) or high-dose adalimumab (160 mg at weeks 0, 1, 2, and 3, and then 40 mg every other week).[11] The primary outcome, clinical remission at week 4, was not different in the 2 treatment groups. In addition, there were no significant differences in endoscopic response over time and in a number of other secondary outcome measures. Again, this was predominantly an anti-TNF–naive patient population.

For both ulcerative colitis and Crohn's disease, the SERENE trials showed that the current FDA-approved dosing regimen is effective and that more intensive induction therapy does not improve outcomes over time. Thus, there is no utility in giving high induction doses.

## Ustekinumab

Ustekinumab was recently approved in both the United States and Europe for ulcerative colitis and has been approved since 2016 for Crohn's disease. At the ACG 2019 meeting, I presented results from a study looking at histologic improvement with ustekinumab in ulcerative colitis patients. In this trial, which consisted of secondary and exploratory endpoints from the pivotal study of ustekinumab for ulcerative colitis, patients received intravenous induction therapy with ustekinumab (approximately 6 mg/kg or 130 mg).[12] Patients who responded to ustekinumab were re-randomized to continue maintenance therapy with subcutaneous ustekinumab (90 mg given either every 8 or 12 weeks) or placebo (meaning that they were withdrawing from ustekinumab after induction with the drug). Patients underwent endoscopy at the end of induction (ie, at 8 weeks), and then again after 44 weeks of maintenance therapy at week 52. They were assessed for clinical remission, endoscopic remission, and histologic remission.

Essentially, we found that subcutaneous ustekinumab achieved higher rates of endoscopic improvement and histologic improvement, as well as histo-endoscopic mucosal healing, which is a composite term describing patients in both an endoscopic improved or remission state

and a histologic improved or remission state. Histo-endoscopic mucosal healing occurred more frequently if patients were receiving maintenance ustekinumab than placebo, and both endoscopic improvement and histologic improvement were associated with clinical remission and corticosteroid-free remission at late endpoints. Thus, at the end of induction, if patients had endoscopic improvement and especially histologic improvement, then they were more likely to have clinical remission and corticosteroid-free remission at week 52.

Doctors have long wondered about the importance of histologic endpoints in ulcerative colitis. We are used to treating to clinical remission, and perhaps endoscopic remission, but not to histologic remission. The data from this study suggest that going all the way to histologic remission provides better clinical outcome measures of clinical remission and corticosteroid-free remission at the end of a year.

## Tofacitinib

Several abstracts were presented at UEG Week 2019 and the ACG 2019 meeting on the use of the Janus kinase inhibitor tofacitinib, which was approved last year for moderate to severe ulcerative colitis. At UEG Week 2019, Dr Edward V. Loftus Jr presented the results of an interim analysis of an open-label, long-term extension study with up to 5.5 years of therapy with tofacitinib, which showed that the drug was generally well tolerated.[13] There were increased risks of serious infections, herpes zoster, and nonmelanoma skin cancer, but those risks are well known and no new toxicity signals were identified.

Another abstract on tofacitinib, which I presented at the ACG 2019 meeting, involved the risk of deep vein thrombosis and pulmonary emboli events in patients who were receiving tofacitinib in the ulcerative colitis clinical development program for the drug.[14] Over 1000 patients who had been treated with tofacitinib were examined. My colleagues and I found that during induction and maintenance of the placebo-controlled portion of the tofacitinib clinical trials, there were a total of 5 deep vein thrombosis and pulmonary emboli events. All 5 occurred in patients who were receiving placebo; none of these events occurred in patients who were receiving tofacitinib. In addition, in a long-term extension trial with tofacitinib, approximately 85% of the exposure was to tofacitinib 10 mg twice daily, and the balance was to tofacitinib 5 mg twice daily. There was a total of 5 deep vein thrombosis and pulmonary emboli events during this long-term extension. There was no control group, but we know from the blinded induction and maintenance phases of the trial that deep vein thrombosis and pulmonary emboli events can be seen on placebo in moderate to severe ulcerative colitis patients. The incidence rates per 100 patient years at follow-up were relatively low. This is generally consistent with what has been seen in other studies in the ulcerative colitis population.[15,16]

These findings are important because there was a study of tofacitinib in patients age 50 years or older with rheumatoid arthritis, as compared to ulcerative colitis, who had 1 or more cardiovascular risk factors.[17] The patients were randomized to anti-TNF therapy with adalimumab 40 mg every other week vs tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily. The data safety monitoring committee reported that there was an excess of deep vein thrombosis and pulmonary emboli events and mortality in the 10-mg twice-daily group. That arm of the trial was halted, and the 5-mg twice-daily and adalimumab arms continued. Based on these data, the FDA changed the labeling of tofacitinib to restrict it to patients who have failed anti-TNF agents, and to require that patients who respond to the 10-mg induction dose of tofacitinib and continue to maintenance make an attempt to drop down to the 5-mg twice-daily dose and be assessed for their other risks of deep vein thrombosis and pulmonary emboli.[18] Looking at the ulcerative colitis clinical trial data that I presented, it is somewhat reassuring that we did not see the same elevation in risk for deep vein thrombosis and pulmonary emboli that was seen in the high-risk rheumatoid arthritis patient population.

***Disclosure***

*Dr Sandborn has received research support from and is a consultant for Takeda Pharmaceuticals, AbbVie, Janssen, and Pfizer.*

## References

1. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med.* 2019;381(13):1215-1226.
2. Danese S, Loftus EV, Colombel JF, et al. Early clinical response and remission with vedolizumab versus adalimumab in ulcerative colitis: results from VARSITY [ACG abstract P0524]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
3. Peyrin-Biroulet L, Colombel JF, Loftus EV, et al. Histologic improvement with vedolizumab vs. adalimumab in ulcerative colitis: results from VARSITY [ACG abstract P1402]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
4. Bressler B, Yarur A, Kopylov U, et al. Clinical effectiveness of first-line anti-TNF therapies and second-line anti-TNF therapy post-vedolizumab discontinuation in patients with ulcerative colitis or Crohn's disease [ACG abstract 40]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
5. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369(8):699-710.
6. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2013;369(8):711-721.
7. Yarur A, Mantzaris GJ, Kopylov U, et al. Real world safety of vedolizumab and anti-TNF therapies in biologic-naïve ulcerative colitis and Crohn's disease patients: results from the EVOLVE study [ACG abstract P2280]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
8. Chambers C, Adams J, Johnson D, Xu R, Luo Y, Lyons-Jones K. The vedolizumab pregnancy exposure registry: an OTIS pregnancy study update [ACG abstract P0525]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
9. Sarles HE, Whitney AE, Kuten SA, Van Anglen LJ. Long-term efficacy of vedolizumab in pediatric inflammatory bowel disease [ACG abstract P1685]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.

10. Panés J, Colombel JF, D'Haens G, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active ulcerative colitis: results from the SERENE-UC induction study [UEG Week abstract OP216]. *United European Gastroenterol J*. 2019;7(8 suppl).
11. D'Haens G, Sandborn WJ, Loftus EV, et al. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active Crohn's disease: results from the SERENE-CD induction study [UEG Week abstract LB27]. *United European Gastroenterol J*. 2019;7(8 suppl).
12. Li K, Friedman JR, Marano C, et al. Effects of ustekinumab maintenance therapy on endoscopic improvement and histologic improvement in the UNIFI phase 3 study in ulcerative colitis [ACG abstract 56]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
13. Lichtenstein GR, Loftus Jr EV, Soonasra A, et al. Tofacitinib, an oral Janus kinase inhibitor, in the treatment of ulcerative colitis: an interim analysis of an open-label, long-term extension study with up to 5.5 years of treatment [UEG Week abstract OP213]. *United European Gastroenterol J*. 2019;7(8 suppl).
14. Sandborn WJ, Panes J, Sands BE, et al. Incidence of venous thromboembolic events in patients with ulcerative colitis treated with tofacitinib in the ulcerative colitis clinical development program [ACG abstract 59]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 25-30, 2019; San Antonio, TX.
15. Weng MT, Park SH, Matsuoka K, et al. Incidence and risk factor analysis of thromboembolic events in East Asian patients with inflammatory bowel disease, a multinational collaborative study. *Inflamm Bowel Dis.* 2018;24(8):1791-1800.
16. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemost.* 2001;85(3):430-434.
17. US Food and Drug Administration. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. https://www.fda.gov/drugs/drug-safety-and-availability/safety-trial-finds-risk-blood-clots-lungs-and-death-higher-dose-tofacitinib-xeljanz-xeljanz-xr. Published February 25, 2019. Accessed November 21, 2019.
18. US Food and Drug Administration. FDA approves boxed warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and. Published July 26, 2019. Accessed November 21, 2019.

G&H