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

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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

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 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.

It Began

Entyvio combines:

LONG-TERM REMISSION

UC and CD patients achieved remission at 52 weeks vs placebo in study populations that included bio-naïve and anti-TNFα-experienced patients2,3

Individual results may vary.

NEW ENGLAND JOURNAL OF MEDICINE

NOW AVAILABLE

*HUMIRA® AbbVie Inc. North Chicago, IL.
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.  

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; TNF = tumor necrosis factor; UC = ulcerative colitis.


**Safeguard Clinical Response with ENTYVIO**

- **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.

- **SAFETY**

  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.

- **SELECTIVITY**

  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.

- **GUT**

  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.

**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.

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

**THE FIRST HEAD-TO-HEAD STUDY of biologic therapies in UC**

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

*HUMIRA* AbbVie Inc. North Chicago, IL.
CONTRAINDICATIONS

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

ADVERSE REACTIONS

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 dyspea, bronchospasm, urticaria, flushing, rash and increased 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 anab 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].

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).

Serious adverse reactions were reported in 7% of patients treated with ENTYVIO and 4% with placebo (UC Trials I and II and CD Trials I and III) compared with 4% of patients treated with placebo (UC Trials I and II and CD Trials I and III).

Serious adverse reactions reported in >1% of patients treated with ENTYVIO 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).
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 the open-label extension 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, transitional cell carcinoma, colon cancer, colon cancer of metastatic adenocarcinoma, renal carcinoma, 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 any 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 incidence 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.

Table 2. Adverse Reactions in ≥2% of ENTYVIO-Treated Patients and ≥1% Higher than in Placebo (UC Trials I and II and CD Trials I and III)∗

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

*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.

In controlled trials, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepis, Listeria meningitis, giardiasis and cytomegaloviral colitis. Whenever possible, physicians were allowed to pretreat with standard medical treatment (e.g., antibiotics, hydrocortisone and/or acyclovir) prior to next infusion.
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.
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. 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.

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.](image-url)
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.

**References**


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**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.
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. 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. 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...
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

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

T he 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
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). 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**

**Table.** Results for Secondary Efficacy Endpoints

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

HIR, higher induction regimen; IBDQ, Inflammatory Bowel Disease Questionnaire; RBS, rectal bleeding score; SIR, standard induction regimen. *Endoscopy scored via a central reading protocol. 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. Nominal P-value <.05. Adapted from Panés J et al. UEG Week abstract OP216. *United European Gastroenterol J*. 2019;7(8 suppl).

**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 α4β7 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. 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. 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-
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 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

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.

*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

**Clinical Remission**

<table>
<thead>
<tr>
<th>Week 14</th>
<th>Week 0</th>
<th>Week 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIBLE 1</td>
<td>VISIBLE OLE</td>
<td></td>
</tr>
<tr>
<td>46.9%</td>
<td>57.0%</td>
<td>39.2%</td>
</tr>
<tr>
<td>67/143</td>
<td>61/107</td>
<td>40/102*</td>
</tr>
</tbody>
</table>

**Clinical Response**

<table>
<thead>
<tr>
<th>Week 14</th>
<th>Week 0</th>
<th>Week 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISIBLE 1</td>
<td>VISIBLE OLE</td>
<td></td>
</tr>
<tr>
<td>79.7</td>
<td>93.5</td>
<td>48.0</td>
</tr>
<tr>
<td>114/143</td>
<td>100/107</td>
<td>49/102*</td>
</tr>
</tbody>
</table>
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
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.

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 (150 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 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...
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; \( P = .0135 \)), histoscop-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%; \( P < .0001 \)), histoscop-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.

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-Naïve 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.

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], 0.46; 95% CI, 0.27-0.71; 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).

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

References
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. 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 91.7

Figure 7. 2Lb anti-TNF effectiveness in UC and CD. CD, Crohn’s disease; TNF, tumor necrosis factor; UC, ulcerative colitis; 1L, first-line; 2L, second-line. *n at risk. bAnti-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
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. 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. 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 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
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. 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

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

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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. 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. 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). 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). 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). 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). 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.13 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**

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**References**

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.