

## A SPECIAL MEETING REVIEW EDITION

### Highlights in IBD From the American College of Gastroenterology 2018 Annual Scientific Meeting and United European Gastroenterology Week 2018

A Review of Selected Presentations From the ACG 2018 Meeting

• October 5-10, 2018 • Philadelphia, Pennsylvania and  
UEG Week 2018 • October 20-24, 2018 • Vienna, Austria

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#### Special Reporting on:

- Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients (EVOLVE)
- Efficacy and Safety of a New Vedolizumab Subcutaneous Formulation for Ulcerative Colitis: Results of the VISIBLE 1 Phase 3 Trial
- A Randomized, Double-Blind, Placebo-Controlled Trial of a Selective Oral Sphingosine 1 Phosphate Receptor Modulator Etrasimod in Moderate to Severe Ulcerative Colitis: Results From the OASIS Study
- Real-World Mucosal Healing With Vedolizumab in Crohn's Disease: A Systematic Review and Meta-Analysis
- Ustekinumab as Induction Therapy in Ulcerative Colitis and With and Without Concomitant Immunosuppressants for Crohn's Disease: Results From the Phase 3 UNIFI Study and the IM-UNITI Long-Term Extension Through 2 Years
- Shifts in Vedolizumab Utilization Across the United States Are Associated With Improved Outcomes
- 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 4.9 Years of Treatment
- Real-World Treatment Persistence With Vedolizumab in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis
- Efficacy and Safety of Upadacitinib as an Induction Therapy for Patients With Moderately to Severely Active Ulcerative Colitis: Data From the Phase 2b Study U-ACHIEVE

#### PLUS Meeting Abstract Summaries

#### With Expert Commentary by:

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# It Began With...



**Entyvio**<sup>®</sup>  
vedolizumab

## In UC & Crohn's

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

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

Only Entyvio combines:

**LONG-TERM** — **AND** — **REMISSION**

UC and CD patients achieved remission at 52 weeks vs placebo in study populations that included bio-naïve and anti-TNF $\alpha$ -experienced patients<sup>1,2</sup>

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.



## GUT SELECTIVITY<sup>3-8</sup>

Entyvio helps address inflammation where it occurs—in the gut

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

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<sup>1,9</sup>

### IMPORTANT SAFETY INFORMATION (continued)

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

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

**Please see brief summary of Prescribing Information on adjacent pages.**

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

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

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## BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

### ENTYVIO (vedolizumab) for injection, for intravenous use

#### INDICATIONS AND USAGE

##### Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

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

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

##### Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

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

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

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

##### Infusion-Related Reactions and Hypersensitivity Reactions

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

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

##### Infections

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

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

##### Progressive Multifocal Leukoencephalopathy

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

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

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

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

##### Liver Injury

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

##### Live and Oral Vaccines

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

#### ADVERSE REACTIONS

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

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

##### Clinical Trials Experience

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

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

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

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

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

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

**Table 2. Adverse Reactions in ≥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 <sup>†</sup> (N=1434)	Placebo <sup>‡</sup> (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.

<sup>†</sup>Patients who received ENTYVIO for up to 52 weeks.

<sup>‡</sup>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).

#### Pregnancy Category B:

#### Risk Summary

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

#### Clinical Considerations

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

#### Animal Data

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

### **Nursing Mothers**

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

### **Pediatric Use**

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

### **Geriatric Use**

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

Manufactured by:

**Takeda Pharmaceuticals America, Inc.**

Deerfield, IL 60015

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For more information, go to [www.ENTYVIO.com](http://www.ENTYVIO.com) or call 1-877-825-3327

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## Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients (EVOLVE)

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC), which affects the colonic mucosa, and Crohn's disease (CD), which can affect any portion of the gastrointestinal tract.<sup>1</sup> Treatment for IBD may include aminosalicylates, corticosteroids, immunomodulators, and biologics. Although inhibitors of tumor necrosis factor (TNF) are effective for many patients, some patients are primary nonresponders while others lose their response over time. Vedolizumab is a humanized antibody that selectively binds to  $\alpha 4\beta 7$  integrin, preventing lymphocyte migration into the gut and, thus, reducing gut inflammation.<sup>2</sup> The antibody has been shown to achieve high rates of clinical response and durable remissions, both in clinical trials and in real-world practice, with favorable safety and tolerability.<sup>3-5</sup>

The safety and efficacy of vedolizumab for the treatment of UC and CD patients were demonstrated in the GEMINI series of clinical trials.<sup>6,7</sup> Based on post hoc analyses, outcomes with vedolizumab were superior in patients without prior exposure to biologic therapy vs patients who had failed prior exposure to anti-TNF agents, supporting the use of vedolizumab as first-line treatment.<sup>8-10</sup> However, real-world data in this setting are limited to small cohorts with follow-up times of 1 year or less.

To address the need for real-world data, 2 large, retrospective chart-review studies were conducted at 19 sites in the United States and Canada, and the results were presented at United European Gastroenterology (UEG) Week 2018 and at the American College of Gastroenterology (ACG) 2018 Annual Scientific Meeting.<sup>11,12</sup> The objective was to describe real-world treatment patterns, clinical efficacy, and safety findings in biologic-naive UC and CD patients treated with vedolizumab. The study population

included adult patients with UC or CD with no prior exposure to biologic therapy, all of whom initiated vedolizumab treatment as the standard of care during the eligibility period and had at least 6 months of follow-up data available. Assessments of active disease, clinical response, clinical remission, and mucosal healing were based on predefined, hierarchical algorithms. Although data from the Canadian study were evaluated separately, results from both Canada and the United States were pooled to increase the sample size available for analysis.

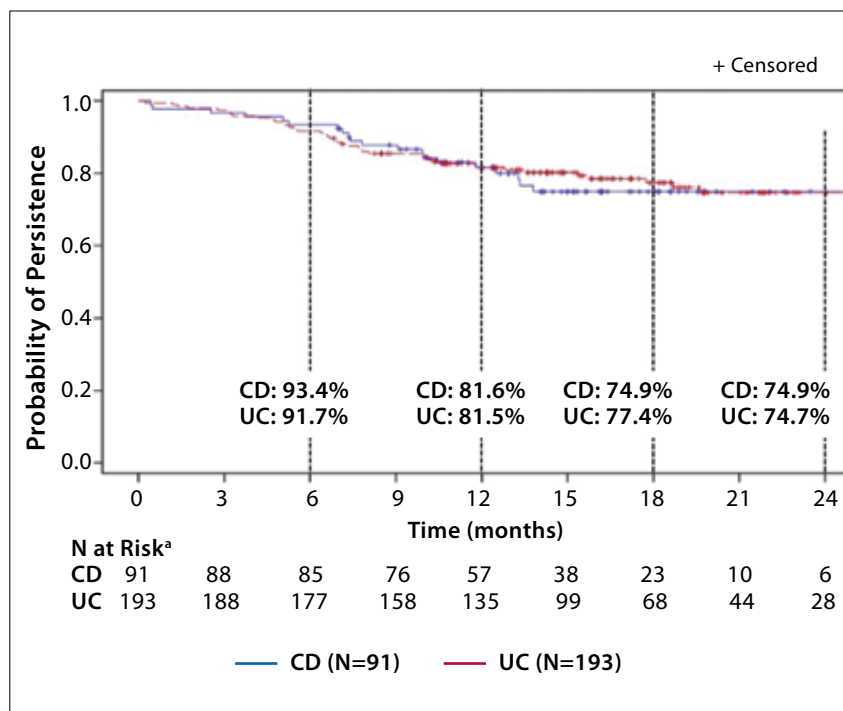
For the interim analysis, the pooled patient population included 284 patients, 193 with UC and 91 with CD.<sup>12</sup> In the UC population, the median age was 42.7 years and 60.6% of patients were male. Median disease duration was approximately 6.0 years (range, 0.1-35.0 years), and median follow-up was 16.8 months (range, 6.4-43.0 months). In the CD population, patients had a median age of 50.0 years, and 55% of patients were men. Median disease duration was approximately 6.8 months (range, 0.1-54.0 months), and median follow-up was 15.6 months (range, 7.0-45.9

months). The median time between disease activity assessment and treatment initiation was 28 days in UC patients and 37 days in CD patients. At initiation of vedolizumab treatment, 88.1% (96/109) of UC patients and 73.7% (42/57) of CD patients had active disease. The primary reasons for selecting vedolizumab treatment were incomplete or no response to prior nonbiologic therapy (UC, 79.8%; CD, 61.5%), anticipated superior safety (UC, 6.7%; CD, 6.6%), and anticipated superior efficacy (UC, 3.1%; CD, 3.3%).

At 18 months, 77.4% of UC patients and 74.9% of CD patients persisted with vedolizumab treatment (Figure 1). Treatment discontinuation occurred in 22.3% of UC patients and 22.0% of CD patients. The majority of discontinuations were due to either primary nonresponse (UC, 11.9%; CD, 9.9%) or secondary loss of response (UC, 9.8%; CD, 4.4%). At 18 months, 22.3% of UC patients and 21.3% of CD patients had experienced a dose escalation. In UC patients at 12 months, the rate of clinical remission was 84.6%, the cumulative probability of remission was 68.4%, and the cumulative prob-

### ABSTRACT SUMMARY Long-Term Safety and Efficacy of Risankizumab Treatment in Patients With Crohn's Disease: Interim Results of the Ongoing Phase 2 Open-Label Extension Study

Efficacy and safety findings were evaluated in an open-label extension study of CD patients treated with maintenance risankizumab (UEG Week abstract OP307). Enrolled patients received open-label risankizumab (180 mg every 8 weeks) for up to 216 weeks. Based on an interim analysis, 65 patients had a median exposure to risankizumab of 689 days (range, 164-900 days), and 14 patients (21.5%) had prematurely discontinued from the study. At week 0, 73.9% of patients were in clinical remission, and 43.1% had endoscopic remission. Clinical remission rates were sustained up to week 48. The proportion of patients with endoscopic remission increased to 53.8% at week 48. No new safety signals were observed.



**Figure 1.** Kaplan-Meier curve for treatment persistence of vedolizumab in bio-naive UC and CD patients. Persistence: patients who remained on vedolizumab during the follow-up period and did not discontinue. Annotated data are the rates at each time point indicated by the dashed line. <sup>a</sup>Number of patients still on vedolizumab at risk for discontinuation. CD, Crohn's disease; UC, ulcerative colitis.

Adapted from Yarur A et al. ACG abstract P1356. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

ability of mucosal healing was 51.0%. In CD patients at 12 months, the rate of clinical remission was 70.3%, the cumulative probability of remission was 52.8%, and the cumulative probability of mucosal healing was 51.0%. Among patients with available data,

81.3% of UC patients (61/75) and 81.2% of CD patients (13/16) were able to discontinue concomitant corticosteroid use during their treatment with vedolizumab. Safety outcomes were similar to those observed in prior studies.

## Efficacy and Safety of a New Vedolizumab Subcutaneous Formulation for Ulcerative Colitis: Results of the VISIBLE 1 Phase 3 Trial

Vedolizumab is available as an intravenous (IV) formulation that is associated with high rates of clinical response and durable remissions as well as favorable safety and tolerability.<sup>1-3</sup> Vedolizumab subcutaneous (SC) is a new liquid formula-

tion of the antibody, developed to provide a more convenient administration option.

The phase 3, double-blind VISIBLE 1 (Efficacy and Safety of Vedolizumab Subcutaneously [SC] as Maintenance Therapy in Ulcerative Colitis)

## References

1. Scribano ML. Vedolizumab for inflammatory bowel disease: from randomized controlled trials to real-life evidence. *World J Gastroenterol.* 2018;24(23):2457-2467.
2. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. *J Crohns Colitis.* 2016;10(12):1437-1444.
3. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut.* 2017;66(5):839-851.
4. 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.
5. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis.* 2015;21(12):2879-2885.
6. Loftus EV Jr, Colombel JF, Feagan BG, et al. Long-term efficacy of vedolizumab for ulcerative colitis. *J Crohns Colitis.* 2017;11(4):400-411.
7. Vermeire S, Loftus EV Jr, Colombel JF, et al. Long-term efficacy of vedolizumab for Crohn's disease. *J Crohns Colitis.* 2017;11(4):412-424.
8. Feagan BG, Lasch K, Lissos T, et al. Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases [published online May 29, 2018]. *Clin Gastroenterol Hepatol.* doi:10.1016/j.cgh.2018.05.026.
9. 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.
10. 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.
11. Bressler B, Bassell M, Stein D, et al. Vedolizumab outcomes in real-world bio-naive ulcerative colitis and Crohn's disease patients (EVOLVE) in Canada: treatment patterns, clinical effectiveness and safety [UEG Week abstract P0353]. *United European Gastroenterol J.* 2018;6(suppl 1).
12. Yarur A, Bassell M, Stein D, et al. Vedolizumab outcomes in real-world bio-naive ulcerative colitis and Crohn's disease patients (EVOLVE) in North America [ACG abstract P1356]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

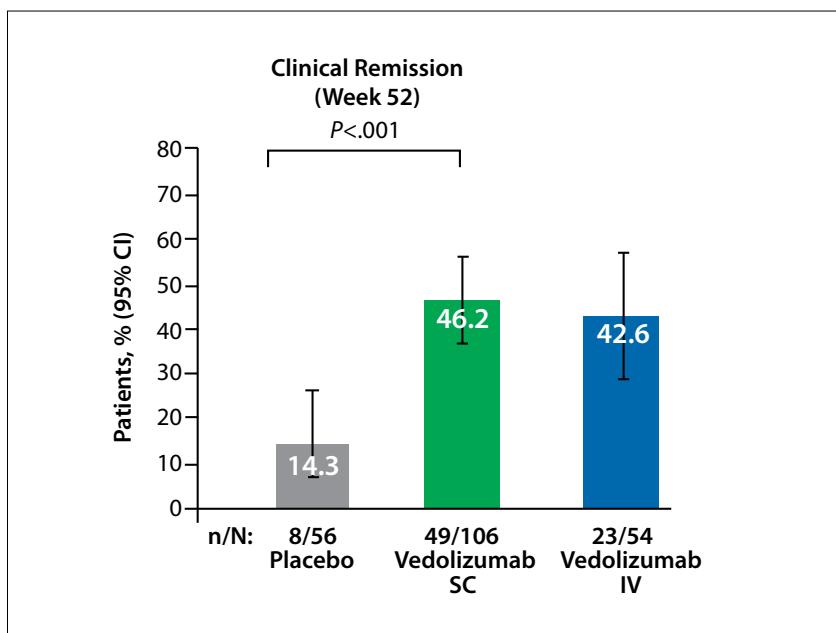


immunomodulatory agents, or anti-TNF therapy. All patients received open-label vedolizumab IV (300 mg) at weeks 0 and 2. Patients were randomized into 3 arms for maintenance therapy. Patients in the placebo arm received placebo SC (every 2 weeks) plus placebo IV (every 8 weeks). Patients in the IV arm received vedolizumab IV (300 mg every 8 weeks) plus placebo SC (every 2 weeks). Patients in the SC arm received vedolizumab SC (108 mg every 2 weeks) plus placebo IV (every 8 weeks). The primary endpoint was clinical remission at week 52, with central reading of all endoscopy results.

The study included 56 patients in the placebo arm, 54 patients in the IV arm, and 106 patients in the SC arm. The mean age was 39.4 years in the placebo arm, 41.6 years in the IV arm, and 38.1 years in the SC arm. Across the 3 arms, the mean duration of UC ranged from 7.4 to 8.2 years, and the proportion of patients with prior anti-TNF use ranged from 35.7% to 44.4%. Only 62.5% of patients in the placebo arm completed study treatment, with 80% of those who discontinued citing lack of efficacy as the reason for stopping treatment. In the IV and SC arms, 24.1% and 27.4% of patients discontinued, respectively, and among those who discontinued, 46.2% in the IV arm and 62.1% in the SC arm cited lack of efficacy as the reason for discontinuation. The rate of clinical remission at week 52 was 14.3% in the placebo arm vs 46.2% in the SC arm ( $P < .001$ )—thus reaching the primary endpoint—and was 42.6% in the IV arm (Figure 2). The proportion of patients with mucosal healing at week 52 was 21.4% in the placebo arm vs 56.6% in the SC arm ( $P < .001$ ) and 53.7% in the IV arm. Durable clinical responses at week 52 were observed in 28.6% of patients in the placebo arm vs 64.2% in the SC arm ( $P < .001$ ) and 72.2% in the IV arm. Vedolizumab SC was superior to placebo in patients without ( $P < .001$ ) or with prior failure to anti-TNF

### ABSTRACT SUMMARY Magnetic Resonance Enterography Assessment of Mucosal Healing With Vedolizumab in Patients With Moderate to Severe Crohn's Disease: Results From the VERSIFY Study

Based on a protocol amendment, the single-arm phase 3 VERSIFY (Effect of Intravenous [IV] Vedolizumab on Mucosal Healing in Crohn's Disease) study was extended to allow vedolizumab treatment to 52 weeks in patients with moderate to severe CD (UEG Week abstract OP175). Endoscopic remission was evaluated by magnetic resonance enterography. Among 37 patients, 32 in the full analysis set completed treatment at week 26, and 21 completed treatment at week 52. The response rate among patients with a Magnetic Resonance Index of Activity (MaRIA)-11 score at baseline was 34% at week 26 and 43% at week 52. In patients with a MaRIA-7 score at baseline, the remission rate was 22% at week 26 and 38% at week 52. A moderate correlation was observed between MaRIA score and changes in endoscopic assessment.



**Figure 2.** The primary efficacy endpoint of clinical remission at week 52 for patients receiving placebo, vedolizumab SC, and vedolizumab IV. Clinical remission: complete Mayo score of  $\leq 2$  points and no individual subscore  $> 1$  point. IV, intravenous; SC, subcutaneous.

Adapted from Sandborn WJ et al. UEG Week abstract LB03. *United European Gastroenterol J.* 2018;6(suppl 1).

treatment ( $P = .023$ ). Vedolizumab SC was generally well tolerated.

### References

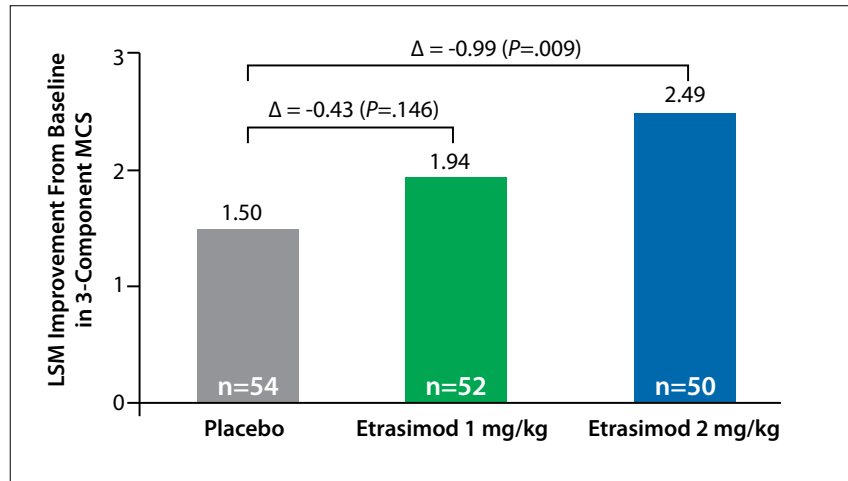
- Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut.* 2017;66(5):839-851.
- Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for

- ulcerative colitis. *N Engl J Med.* 2013;369(8):699-710.
- Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. *Inflamm Bowel Dis.* 2015;21(12):2879-2885.
- Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of a new vedolizumab subcutaneous formulation for ulcerative colitis: results of the VISIBLE 1 phase 3 trial [UEG Week abstract LB03]. *United European Gastroenterol J.* 2018;6(suppl 1).

## A Randomized, Double-Blind, Placebo-Controlled Trial of a Selective Oral Sphingosine 1 Phosphate Receptor Modulator Etrasimod in Moderate to Severe Ulcerative Colitis: Results From the OASIS Study

Etrasimod is an oral sphingosine 1 phosphate receptor modulator.<sup>1,2</sup> In phase 1 research, etrasimod elicited a dose-dependent reduction in total peripheral lymphocyte counts, with reductions in T-naive and T-central memory cells.<sup>3</sup> The drug was generally well tolerated when administered at up to 2 mg once daily. At the ACG 2018 meeting, results were presented from the phase 2 OASIS (Safety and Efficacy of Etrasimod [APD334] in Patients With Ulcerative Colitis) trial, which evaluated etrasimod in adult patients with moderate to severe UC.<sup>4</sup> Patients were evenly randomized to receive placebo, etrasimod 1 mg/kg, or etrasimod 2 mg/kg during a 12-week induction phase. The primary endpoint was improvement in the Mayo Clinic score at week 12.

The study enrolled 156 patients. Across the 3 arms, the mean duration of UC ranged from 6.2 to 8.6 years, and the mean Mayo Clinic score ranged from 8.7 to 8.9. After 12 weeks of treatment, the Mayo Clinic score improved from baseline by 1.50 in the placebo arm, by 1.94 ( $P=.146$ ) in the etrasimod 1-mg/kg arm, and by 2.49 ( $P=.009$ ) in the etrasimod 2-mg/kg arm (Figure 3). The rate of endoscopic improvement at week 12 was 17.8% with placebo, 22.5% with the lower dose of etrasimod ( $P=.306$ ), and 41.8% with the higher dose of etrasimod ( $P=.003$ ). The rate of endoscopic remission, an exploratory endpoint, was 5.3% with placebo, 13.7% with etrasimod 1 mg/kg ( $P=.089$ ), and 15.3% with etrasimod 2 mg/kg ( $P=.049$ ). Other exploratory endpoints, including clinical remission and clinical response based on the Mayo Clinic score, showed a significant benefit with etrasimod 2 mg/kg vs placebo, but not with the lower dose



**Figure 3.** The primary endpoint was 3-component MCS improvement at week 12 (rectal bleeding, stool frequency, and endoscopy).  $\Delta$  is the LSM difference from placebo. LSM was estimated using an analysis of covariance model that included current oral corticosteroid therapy at baseline and previous exposure to tumor necrosis factor antagonists, baseline measure, and treatment group. LSM, least squares mean; MCS, Mayo Clinic score.

Adapted from Sandborn WJ et al. ACG abstract 11. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

### ABSTRACT SUMMARY Results From the Vedolizumab Pregnancy Exposure Registry: An OTIS Pregnancy Study

The Vedolizumab Pregnancy Exposure Registry is collecting information from patients in the United States and Canada in order to evaluate the effect of vedolizumab treatment in pregnant women (ACG abstract P2257). The prospective, observational cohort study will evaluate outcomes in 100 pregnant women exposed to vedolizumab for comparison with 100 disease-matched patients and 100 healthy participants. Enrolled patients were treated with vedolizumab for their UC or CD for at least part of the first trimester. The study has enrolled 28 pregnant women with vedolizumab exposure, 52 disease-matched patients, and 63 healthy controls. Among the 28 vedolizumab-exposed pregnant women, 92.9% had exposure to vedolizumab in the first, second, and third trimesters. Available data suggest that birth outcomes in pregnant women exposed to vedolizumab during the first trimester are similar to those of disease-matched and healthy control women.

of etrasimod. Rectal bleeding scores improved significantly over time in both etrasimod arms compared with placebo ( $P<.05$ ), and dose-dependent reductions in lymphocyte counts were observed in both etrasimod arms

( $P < .001$ ). Etrasimod was generally well tolerated.

## References

1. Peyrin-Biroulet L, Christopher R, Behan D, Lassen C. Modulation of sphingosine-1-phosphate in inflammatory bowel disease. *Autoimmun Rev*. 2017;16(5):495-503.
2. Buzard DJ, Kim SH, Lopez L, et al. Discovery of

APD334: design of a clinical stage functional antagonist of the sphingosine-1-phosphate-1 receptor. *ACS Med Chem Lett*. 2014;5(12):1313-1317.

3. Peyrin-Biroulet L, Adams J, Turner S, Panes J. Safety and immune modulatory properties of etrasimod (APD334), a next-generation oral, selective sphingosine 1-phosphate receptor (S1PR) modulator, in healthy volunteers [ECCO abstract P573]. Presented at the 13th Congress of the European Crohn's and Colitis Organization; September 7-9, 2018; Vienna, Austria.

Vienna, Austria.

4. Sandborn WJ, Peyrin-Biroulet L, Trokan L, et al. A randomized, double-blind, placebo-controlled trial of a selective oral sphingosine 1 phosphate receptor modulator etrasimod in moderate to severe ulcerative colitis: results from the OASIS study [ACG abstract 11]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

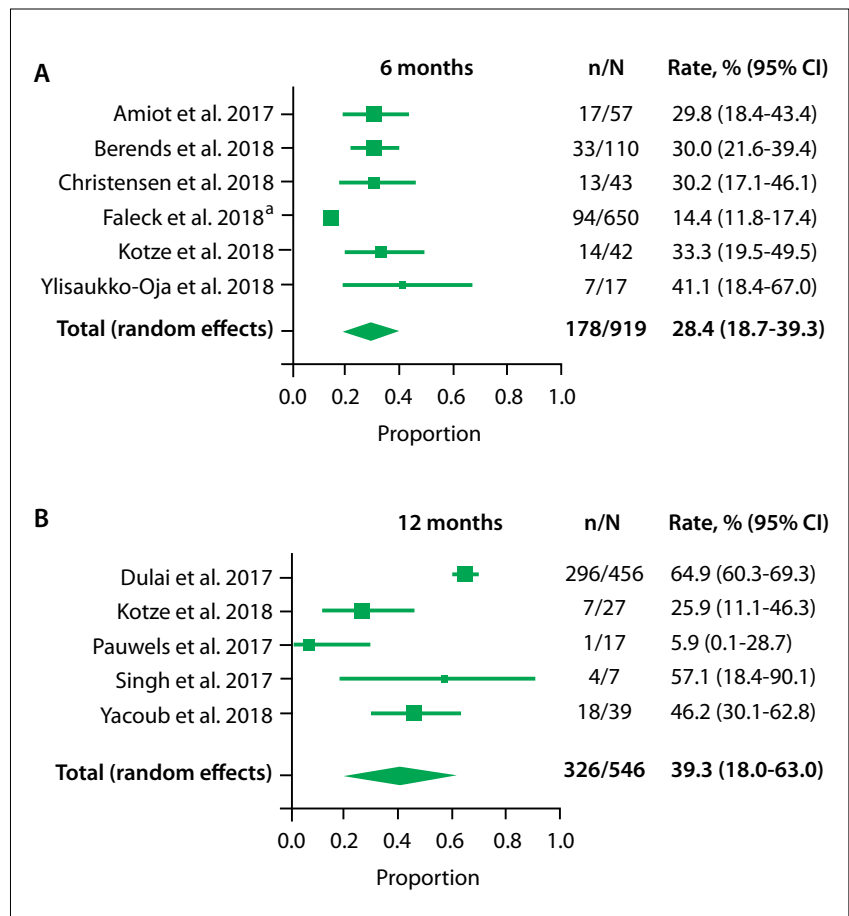
## Real-World Mucosal Healing With Vedolizumab in Crohn's Disease: A Systematic Review and Meta-Analysis

For CD patients, mucosal healing is correlated with improved clinical outcomes and is a recommended goal of therapy.<sup>1-3</sup> Results from several real-world studies suggest that vedolizumab may promote mucosal healing.<sup>4</sup> To further elucidate these findings, a systematic review and meta-analysis were conducted encompassing global, real-world mucosal healing rates in CD patients treated with vedolizumab, and the findings were presented at the ACG 2018 meeting.<sup>5</sup> A comprehensive literature search identified all real-world studies that reported data on mucosal healing/endoscopic remission and/or endoscopic response in CD patients treated with vedolizumab. Reports in pediatric patients and reports with a sample size of fewer than 10 patients were excluded.

Among 3163 articles originally identified, 24 studies met the inclusion criteria. Among the included studies, patient median age ranged from 34 to 49 years, and median disease duration ranged from 2 to 16 years. In studies that included patients with prior exposure to biologic agents, between 64% and 99% of the participants had prior exposure to anti-TNF therapy. The study population size ranged from 17 to 650 patients. Twelve studies defined mucosal healing as the absence of all ulcers and/or erosions, whereas other studies relied on endoscopy scores. Analyses of pooled data from 11 studies yielded mucosal healing rates of 28.4% (95% CI, 18.7%-

39.3%;  $I^2=85%$ ) at 6 months (n=919) and 39.3% (95% CI, 18.0%-63.0%;  $I^2=91%$ ) at 12 months (n=546; Figure 4). Three studies reported mucosal

healing rates in biologic-naive patients only, and pooled mucosal healing rates from these patients ranged from 46% to 63% at 6 months, with 1



**Figure 4.** Meta-analysis of mucosal healing rates at 6 months (A) and 12 months (B) with vedolizumab in Crohn's disease. Size of the box in the forest plot represents the study sample size. <sup>a</sup>Combined data from the <2-year and ≥2-year cohorts.

Adapted from Danese S et al. ACG abstract P2235. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

study yielding a 100% mucosal healing rate at 12 months; however, the reported sample sizes were small, ranging from 2 to 11 patients. The most common definition of endoscopic improvement, used in 6 studies, was a reduction of greater than 50% in Simple Endoscopic Score–CD. Analyses yielded endoscopic improvement rates of 39% to 40% at 6 months (2 studies) and 38% at 12 months (1 study). A single study reported an endoscopic improve-

ment rate of 73% in biologic-naïve patients at 6 months. Despite limitations, the results suggest an association between vedolizumab use and mucosal healing in CD patients in a real-world setting.

### References

1. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113(4):481-517.
2. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel

Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110(9):1324-1338.

3. Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther*. 2016;43(3):317-333.
4. Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol*. 2018;53(9):1048-1064.
5. Danese S, Demuth D, Geransar P, Campbell-Hill S, Irving P. Real-world mucosal healing with vedolizumab in Crohn's disease: a systematic review and meta-analysis [ACG abstract P2235]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

## Ustekinumab as Induction Therapy in Ulcerative Colitis and With and Without Concomitant Immunosuppressants for Crohn's Disease: Results From the Phase 3 UNIFI Study and the IM-UNITI Long-Term Extension Through 2 Years

Ustekinumab is a fully human antibody that binds to the p40 subunit of interleukins 12 and 23, thus normalizing the signaling, cellular activation, and cytokine production associated with inflammation. Presented at the ACG 2018 meeting, the phase 3 UNIFI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Parti-

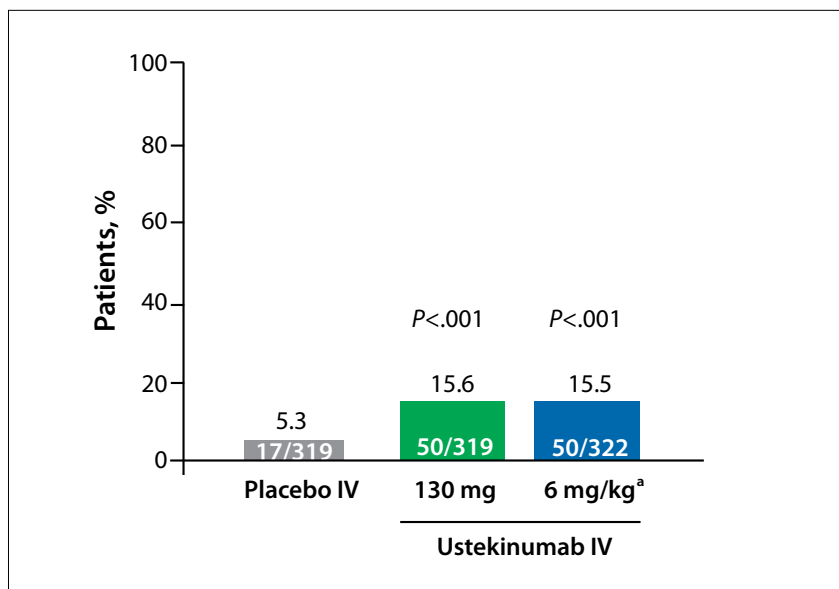
pants With Moderately to Severely Active Ulcerative Colitis) study evaluated the safety and efficacy of ustekinumab induction therapy vs placebo in patients with moderately to severely active UC who had an inadequate response to or were unable to tolerate biologic or conventional therapies.<sup>1</sup> Ustekinumab was administered as a single IV infusion at 130 mg or at approximately

6 mg/kg. The primary endpoint was clinical remission at week 8. The international trial enrolled 961 participants. The median Mayo score at baseline was 9.0, and approximately 15% of patients had a Mayo score greater than 10. The rate of clinical remission at week 8 was 5.3% in the placebo arm, compared with 15.6% in the ustekinumab 130-mg arm and 15.5% in the ustekinumab 6-mg/kg arm ( $P < .001$  for both; Figure 5). The clinical remission rate at week 8 was superior with fixed-dose or weight-based ustekinumab vs placebo, regardless of prior failure to biologic therapy ( $P < .05$ ). Other outcomes that were superior with ustekinumab included endoscopic healing, clinical response, quality of life, and mucosal healing. No new safety signals were raised.

The phase 3 IM-UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Patients With Moderately to Severely Active Crohn's Disease) trial investigated outcomes in patients with moderate to severe CD through 2 years of maintenance therapy.<sup>2</sup> In light of recent findings, the effect of

### ABSTRACT SUMMARY The Intestinally Restricted, Orally Administered, Pan-JAK Inhibitor TD-1473 Demonstrates Favorable Safety, Tolerability, Pharmacokinetics, and Signal for Clinical Activity in Subjects With Moderately to Severely Active Ulcerative Colitis

TD-1473 is a pan-Janus kinase inhibitor that was evaluated in a double-blind, placebo-controlled, phase 1b study of patients with moderately to severely active UC (UEG Week abstract LB05). Three active treatment cohorts received TD-1473 once daily for 28 days at a dose of 20 mg (n=10), 80 mg (n=10), or 270 mg (n=11), and 9 patients received placebo. Patients had a mean Mayo score of 8.9. One patient in the 20-mg cohort discontinued treatment at day 5 due to lack of efficacy. Two serious treatment-emergent AEs occurred. Compared with placebo, TD-1473 treatment was associated with a trend toward improved higher rates of mucosal healing and improvements in rectal bleeding and endoscopy.



**Figure 5.** The primary endpoint was clinical remission at week 8 or Mayo score  $\leq 2$  points with no individual subscore  $> 1$ . Subjects who had a prohibited change in concomitant UC medication or an ostomy or colectomy prior to the week 8 visit were considered not to be in clinical remission. Subjects who had all 4 Mayo subscores missing at week 8 were considered not to be in clinical remission. The  $P$  values were based on the Cochran-Mantel-Haenszel test. <sup>a</sup>Weight range–based ustekinumab doses approximating 6 mg/kg: 260 mg (weight  $\leq 55$  kg), 390 mg (weight  $> 55$  kg and  $\leq 85$  kg), and 520 mg (weight  $> 85$  kg). IV, intravenous; UC, ulcerative colitis.

Adapted from Sands BE et al. ACG abstract 54A. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

concomitant immunomodulator use in patients in the IM-UNITI study during year 2 of ustekinumab maintenance was evaluated, and the results were presented at the ACG 2018 meeting.<sup>3,4</sup> Eighty-two patients received continuous ustekinumab (90 mg every 8 weeks), and 29 of these patients (35%) were using concomitant immunomodulators at baseline. At week 44, the proportion of patients in clinical remission was similar for patients using concomitant immunomodulators (82.8%) and in patients who were not (84.9%). The rates of clinical remission remained

similar through week 92 (72.4% with vs 75.5% without concomitant immunomodulator use). The incidence of antidrug antibodies was similar for patients who were using concomitant immunomodulators (3.4%) and in patients who were not (3.8%;  $P$ =not significant). The median serum concentration of ustekinumab was also similar in both cohorts at all evaluated time points from week 44 through week 92.

### References

1. Sands BE, Sandborn WJ, Panaccione R, et al. Safety and efficacy of ustekinumab induction therapy in patients with moderate to severe ulcerative colitis:

results from the phase 3 UNIFI study [ACG abstract 54A]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

2. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI-IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2016;375(20):1946-1960.

3. Sands BE, Kramer BC, Gasink C, et al. Long-term efficacy and safety of ustekinumab with and without concomitant immunosuppressants for Crohn's disease: results from IM-UNITI long-term extension through two years [ACG abstract 49]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

4. Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. *Gastroenterology.* 2018;154(6):1660-1671.

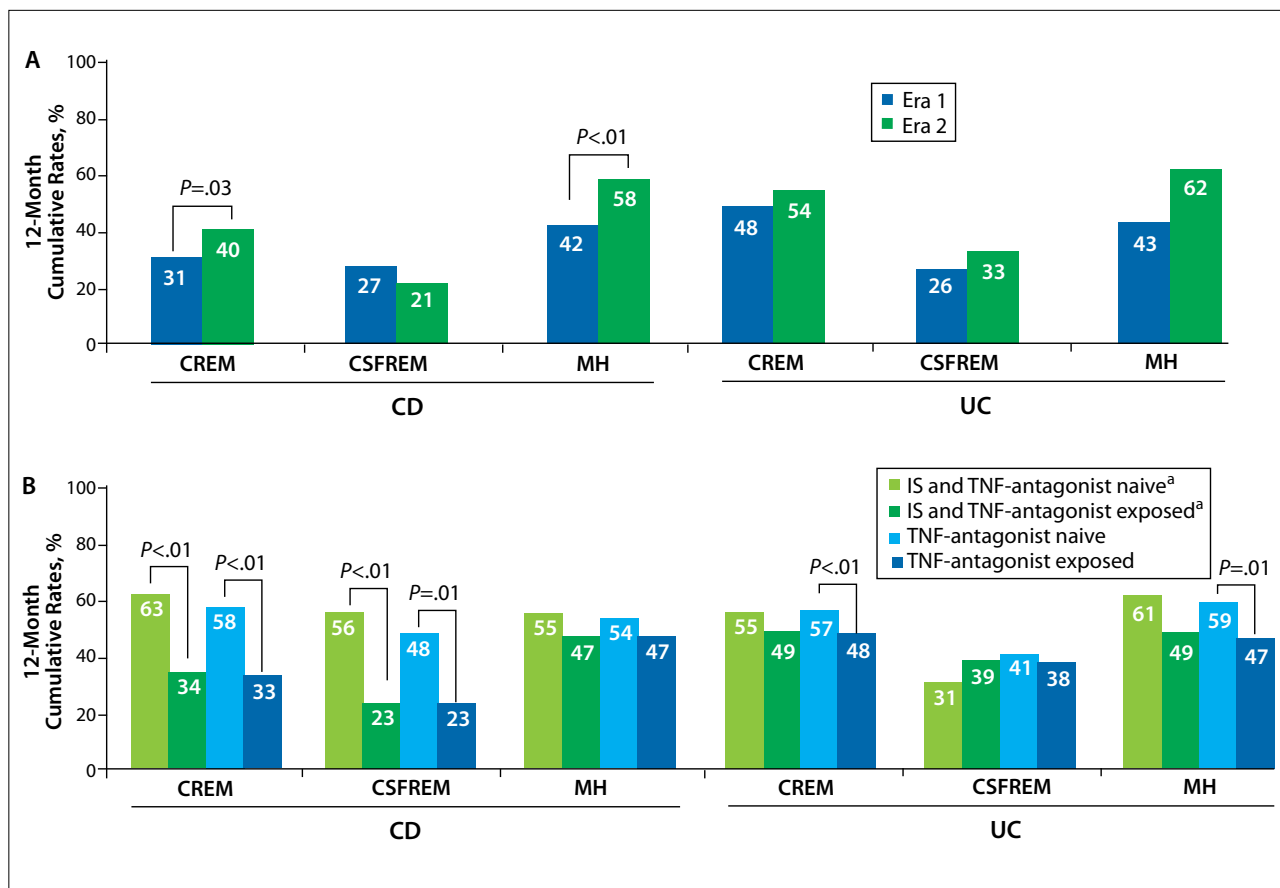
## Shifts in Vedolizumab Utilization Across the United States Are Associated With Improved Outcomes

At the ACG 2018 meeting, results were presented from a study conducted to evaluate vedolizumab utilization patterns and real-world treatment outcomes in IBD patients in the United States during the 3 years after vedolizumab approval by the US Food and Drug Administration (FDA).<sup>1</sup> Data were retrospectively collected from 1087 patients in the VICTORY Consortium, a collabora-

tive cohort study of vedolizumab use in routine clinical practice.<sup>2,3</sup> Data were collected from 2574 additional patients in a nationally representative claims database. A time-trend analysis was performed based on the time since FDA approval. Era 1 included the first 12 months of real-world vedolizumab use after FDA approval (May 2014 through June 2015); Era 2 included the next 24 months (July 2015 through

June 2017).

In the VICTORY cohort, 325 CD patients were treated during Era 1 and the same number of patients were treated during Era 2. One hundred eighty-two UC patients were treated during Era 1, and 255 UC patients were treated during Era 2. In the CD cohort, fewer patients with fistulizing disease were treated during Era 2 (41% vs 32%;  $P=.03$ ). More biologic-naïve



**Figure 6.** Twelve-month effectiveness in the VICTORY cohort in Era 1 and Era 2 (A) and treatment-naive and treatment-exposed patients (B). <sup>a</sup>Azathioprine, methotrexate, 6-mercaptopurine. CD, Crohn's disease; CREM, clinical remission; CSFREM, corticosteroid-free remission; IS, immunosuppressant; MH, mucosal healing; TNF, tumor necrosis factor; UC, ulcerative colitis.

Adapted from Koliani-Pace JL et al. ACG abstract P0444. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

patients were treated during Era 2, both in the CD cohort (2% vs 7%;  $P<.01$ ) and in the UC cohort (12% vs 23%;  $P<.01$ ). In the CD cohort, fewer patients in Era 2 were using concomitant corticosteroids (54% vs 37%;  $P<.01$ ) or concomitant immunosuppressants (46% vs 37%;  $P=.02$ ). In the UC cohort, fewer patients who were using concomitant corticosteroids were treated with vedolizumab (62% vs 50%;  $P=.02$ ), but a similar number of patients were using concomitant immunosuppressants (33% vs 34%;  $P=.92$ ). In the national database cohort, 213 CD patients were treated during Era 1 and 1232 were treated during Era 2, whereas 116 UC patients were treated during Era 1 and 1013 were treated during Era 2. A

similar number of biologic-naive CD patients were treated during both Era 1 and Era 2 (18% vs 20%;  $P=.47$ ), but more biologic-naive UC patients were treated during Era 2 (17% vs 25%;  $P=.05$ ).

In the VICTORY cohort, the 12-month cumulative rate of clinical remission was significantly higher in patients treated during Era 2 ( $P=.03$ ), as was the cumulative rate of mucosal healing ( $P<.01$ ; Figure 6). Several subgroup analyses suggested improved cumulative rates of clinical outcomes in CD and UC patients who had no prior exposure to immunosuppressants and/or TNF antagonists. In the national database cohort, rates of hospitalization and surgery were similar among CD patients treated with vedolizumab

in Era 1 vs Era 2, and no significant differences emerged from subgroup analysis. UC patients treated during Era 2 experienced significantly reduced rates of hospitalization (22.4% vs 9.6%;  $P<.001$ ) and surgery (17.2% vs 9.4%;  $P=.008$ ).

## References

- Koliani-Pace JL, Singh S, Hirten R, et al. Shifts in vedolizumab utilization across the United States are associated with improved outcomes [ACG abstract P0444]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.
- Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY Consortium. *Am J Gastroenterol.* 2016;111(8):1147-1155.
- Narula N, Peerani F, Meserve J, et al. Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY Consortium. *Am J Gastroenterol.* 2018;113(9):1345-1354.

## 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 4.9 Years of Treatment

**T**ofacitinib is an oral Janus kinase inhibitor that is approved in several countries for UC treatment. The safety and efficacy of tofacitinib have been demonstrated in the phase 3 OCTAVE (Oral Clinical Trials for Tofacitinib in Ulcerative Colitis) trials.<sup>1</sup> OCTAVE Open is a long-term extension study. The study has a primary objective of assessing the safety and tolerability of long-term tofacitinib therapy while evaluating long-term efficacy, and an interim analysis was presented at the ACG 2018 meeting.<sup>2</sup> Enrolled patients had participated in prior OCTAVE studies and had either lacked a response, experienced treatment failure, or were not in remission. These patients

(n=769) received tofacitinib (10 mg twice daily) in the OCTAVE Open study. OCTAVE Open also enrolled 175 patients from the OCTAVE Sustain study who were in remission, and these patients received a lower dose of tofacitinib (5 mg twice daily). Patients were allowed to switch to the other dose of tofacitinib after receiving at least 8 weeks of initial treatment.

The median drug exposure was 710 days (range, 36-1533 days) among the patients who received the lower dose of tofacitinib and was 562 days (range, 1-1793 days) in patients who received the higher dose. During the extension study, 32 of the patients who were in remission at study entry increased their dose to 10 mg twice

daily, while 61 (7.9%) of the 769 patients initially assigned to the higher dose of tofacitinib chose to receive a dose reduction to 5 mg twice daily. In the overall study population, the median time since diagnosis was 6.5 years (range, 0.6-42.9 years). Study drug was discontinued in 25.1% of patients in the lower-dose arm and in 58.3% of patients in the higher-dose arm (Table 1). Most discontinuations were due to insufficient clinical response. Rates of adverse events (AEs) were generally similar with either dose of tofacitinib, although the higher dose yielded a numerically higher rate of serious AEs (12.0% vs 15.5%). At 24 months, the lower dose of tofacitinib was associated with a remission rate

**Table 1.** Summary of Safety (FAS)<sup>a</sup>

	Tofacitinib 5 mg BID (N=175)	Tofacitinib 10 mg BID (N=769)	Tofacitinib Total (N=944)
<b>Discontinuations, n (%)</b>	44 (25.1)	448 (58.3)	492 (52.1)
Due to AEs excluding worsening UC <sup>b</sup>	12 (6.9)	53 (6.9)	65 (6.9)
Due to insufficient clinical response			
Prior to, or at, month 2 <sup>c</sup>	0 (0.0)	174 (22.6)	174 (18.4)
OLE data cutoff (Nov 2017; cumulative)	14 (8.0)	312 (40.6)	326 (34.5)
<b>All-causality TEAEs, n (%)</b>			
AEs	138 (78.9)	607 (78.9)	745 (78.9)
Serious AEs	21 (12.0)	119 (15.5)	140 (14.8)
Severe AEs	14 (8.0)	79 (10.3)	93 (9.9)
GI AEs (SOC)	64 (36.6)	321 (41.7)	385 (40.8)
Any infections/infestations (SOC)	91 (52.0)	375 (48.8)	466 (49.4)
<b>All-causality TEAEs by preferred term occurring in ≥10% of patients in any treatment group, n (%)</b>			
Nasopharyngitis	30 (17.1)	143 (18.6)	173 (18.3)
Worsening UC	36 (20.6)	132 (17.2)	168 (17.8)
Blood creatine phosphokinase increased	17 (9.7)	77 (10.0)	94 (10.0)

<sup>a</sup>FAS was defined as all patients who received ≥1 dose of study drug. <sup>b</sup>AEs of worsening UC leading to discontinuation were designated as insufficient clinical response. <sup>c</sup>All patients underwent endoscopy at month 2; induction nonresponders were mandated to discontinue if they did not have evidence of clinical response. AE, adverse event; BID, twice daily; FAS, full analysis set; GI, gastrointestinal; N, number of patients in the treatment group; n, number of unique patients with a particular AE; OLE, open-label, long-term extension; SOC, system organ class; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

Adapted from Lichtenstein GR et al. ACG abstract 13. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

of 78.4%, a mucosal healing rate of 87.8%, and a clinical response rate of 97.7%, while the higher dose of tofacitinib yielded a remission rate of 70.9%, a mucosal healing rate of 80.8%, and a

clinical response rate of 93.9%.

## References

1. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736.

2. Lichtenstein GR, Loftus EV, Bloom S, 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 4.9 years of treatment [ACG abstract 13]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

## Real-World Treatment Persistence With Vedolizumab in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

The ACG 2018 meeting included findings from a systematic review and meta-analysis conducted to determine the real-world treatment persistence in IBD patients treated with vedolizumab.<sup>1</sup> All real-world studies that reported data on vedolizumab persistence or discontinuation rates in IBD patients were included. Studies of pediatric patients, of off-label use of vedolizumab, or with fewer than

10 patients were excluded. Of 2873 identified articles, 16 studies met the inclusion criteria. Of the 16 studies that reported real-world vedolizumab persistence rates, 10 reported on both UC and CD patients; 2 reported on CD patients only; 1 reported on UC patients only; and 3 reported on a combined population of IBD patients. Nine studies reported vedolizumab persistence rates at 6 months, 5 studies reported rates at 12 months, and

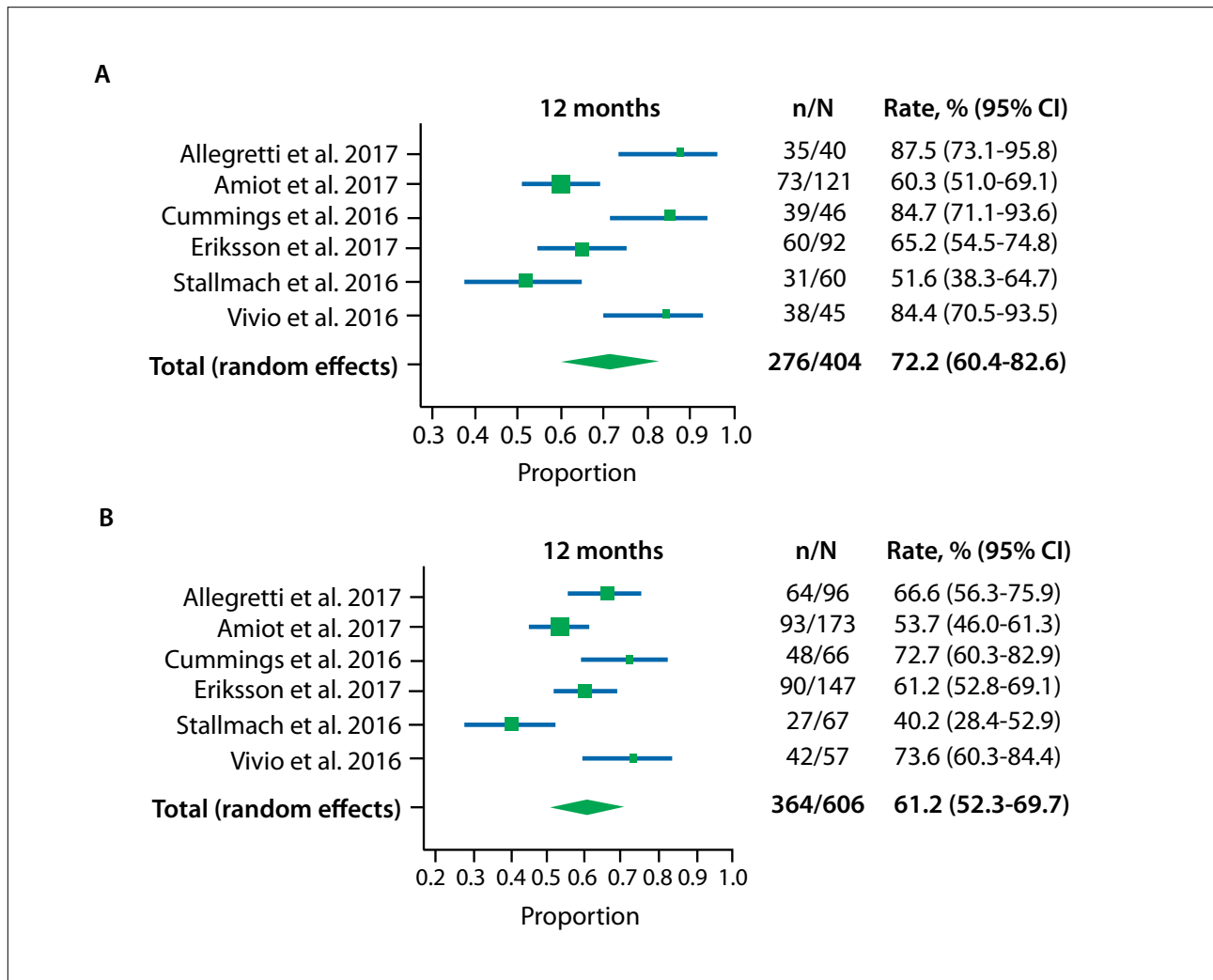
2 studies reported rates at both 6 and 12 months.

Vedolizumab persistence rates at 6 months ranged from 65.2% to 93.5% in 7 studies of UC patients and from 63.6% to 88.4% in 8 studies of CD patients. Two studies of IBD patients reported persistence rates of 38% and 79%. Vedolizumab persistence rates at 12 months ranged from 51.6% to 87.5% in 6 studies of UC patients and from 40.2% to 73.6% in 6 studies of CD patients (Figure 7). A meta-analysis of vedolizumab across all studies at 12 months showed overall vedolizumab persistence rates of 72.2% (95% CI, 60.4%-82.6%;  $I^2=84%$ ) in UC patients and 61.2% (95% CI, 52.3%-69.7%;  $I^2=80%$ ) in CD patients. In a single study with the longest follow-up time, the median follow-up was 17 months (interquartile range, 14-20 months), and the vedolizumab persistence rate was 58% in IBD patients. Among 8 studies that reported reasons for discontinuation, the main reasons for treatment cessation were lack of response and loss of response, while few patients discontinued due to AEs. Regional variation in vedolizumab persistence rates was observed. Vedolizumab treatment persistence rates were highest in a study conducted in the United Kingdom, which reported persistence rates of 94% at 6 months and 85% at 12 months in UC patients, and persistence rates of 77% at 6 months and 73% at 12 months in CD patients. The lowest rates of persistence were observed in a study conducted in Germany, which reported 12-month persistence rates of 52% in UC patients

### ABSTRACT SUMMARY Real-World Effectiveness of Vedolizumab and Anti-Tumor Necrosis Factor Treatment Over 6 Months in Ulcerative Colitis and Crohn's Disease: Two German Retrospective Chart Reviews

The real-world efficacy and safety of vedolizumab in adult IBD patients with or without prior exposure to a biologic agent were evaluated in 2 retrospective multicenter studies in Germany. By week 26 of the UC study (UEG Week abstract P1002), Kaplan-Meier estimates showed a significant increase in clinical remission rate with vedolizumab vs anti-TNF treatment (53.7% vs 31.7%;  $P=.04$ ). The rate of clinical remission was 50.1% with vedolizumab vs 31.5% with anti-TNF treatment among biologic-naive patients and was 55.5% vs 30.7% among patients with prior anti-TNF treatment. Resolution of rectal bleeding was achieved in 68.8% of patients treated with vedolizumab vs 57.0% of those treated with an anti-TNF agent ( $P=.11$ ), while among those with prior anti-TNF exposure, the rate of resolution of rectal bleeding was 65.7% with vedolizumab vs 52.0% with anti-TNF therapy ( $P=.17$ ). Rates of stool frequency resolution were also similar for vedolizumab vs anti-TNF therapy, among both biologic-naive patients and among patients with prior exposure to anti-TNF treatment. By week 26 of the CD study (UEG Week abstract P1589), the rate of clinical remission was 25.0% with vedolizumab vs 33.7% with anti-TNF treatment among biologic-naive patients ( $P=.80$ ) and was 13.0% with vedolizumab vs 33.0% with anti-TNF treatment among patients with prior exposure to anti-TNF therapy ( $P=.06$ ). For rates of resolution of abdominal pain and resolution of liquid stool, no significant differences emerged with vedolizumab vs anti-TNF treatment among patients with vs without prior biologic exposure.





**Figure 7.** Meta-analysis of vedolizumab treatment persistence rates at 12 months in ulcerative colitis (A) and in Crohn's disease (B). Size of the box in the forest plot represents the study sample size.

Adapted from Demuth D et al. ACG abstract P1347. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

and 40% in CD patients. Two publications reported vedolizumab treatment persistence in subgroups of biologic-naïve and -experienced patients, and higher rates of persistence were consistently observed at 6 months in the biologic-naïve cohorts of UC, CD, or IBD patients.

## Reference

1. Demuth D, Patel H, Adsul S. Real-world treatment persistence with vedolizumab in inflammatory bowel disease: a systematic review and meta-analysis [ACG abstract P1347]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

## ABSTRACT SUMMARY Defining Early Disease in Inflammatory Bowel Disease: The Results of a Systematic Literature Review

A systematic literature review was conducted to evaluate definitions of early disease, as applied in clinical and observational studies of UC and CD patients (UEG Week abstract P0351). Included studies were published between January 1, 2008 and March 2, 2018. Among 124 studies, median disease duration in patients with early disease ranged from 0.2 to 16.9 years in UC and from 0.2 to 16.1 years in CD. In studies that provided a definition, early disease was most frequently defined by time since diagnosis or by time since diagnosis and treatment history. Many patients classified as having early disease already showed characteristics of complex disease, suggesting that the opportunity for optimal control of early disease may have been missed.

## Efficacy and Safety of Upadacitinib as an Induction Therapy for Patients With Moderately to Severely Active Ulcerative Colitis: Data From the Phase 2b Study U-ACHIEVE

Upadacitinib is an oral inhibitor of Janus kinase 1. The efficacy and safety of the drug were evaluated in a phase 2b induction study of UC patients, and the findings were presented at UEG Week 2018.<sup>1</sup> The double-blind, placebo-controlled, dose-ranging study enrolled adults with moderately to severely active UC who had an inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressants, or biologic therapy. Patients were randomized to receive placebo or extended-release upadacitinib once daily at a dose of 7.5 mg, 15 mg, 30 mg, or 45 mg for 8 weeks. The primary endpoint was clinical remission based on the adapted Mayo score at week 8, defined as a stool frequency subscore of 1 or less, rectal bleeding subscore of 0, and endoscopic subscore of 1 or less. A dose-response relationship between treatment and primary outcome was evaluated using prespecified candidate models in the intent-to-treat population.

The 250 randomized patients had a mean age of 42.3 years (standard deviation, 14.2 years) and a mean disease duration of 8.2 years (standard deviation, 2.5 years). At baseline, 77.6% of patients had prior exposure to biologic therapy, and 36% had an adapted Mayo score of greater than 7. After 8 weeks of treatment, rates of clinical remission by adapted Mayo score were significantly improved with once-daily upadacitinib administered at 15 mg (14.3%;  $P < .05$ ), 30 mg (13.5%;  $P < .05$ ), or 45 mg (19.6%;  $P < .01$ ) compared with placebo (0%; Table 2). Upadacitinib administered once daily at a dose of 45 mg consistently yielded the highest response rates vs placebo, based on endoscopic improvement (35.7% vs 2.2%;  $P < .001$ ), clinical remission based on the full Mayo score (19.6% vs 0%;  $P < .01$ ), and clinical response based on the adapted Mayo score (50.0% vs 13.0%;  $P < .001$ ). A dose-response relationship was observed

with upadacitinib for the primary and secondary endpoints. Rates of AEs and AEs leading to discontinuation were similar across the 4 upadacitinib doses and were numerically higher in the placebo arm. Rates of serious AEs were 10.9% in the placebo arm, and in the once-daily upadacitinib arms were 0% (7.5 mg), 4.1% (15 mg), 5.8% (30 mg), and 5.4% (45 mg). Serious infections were observed in 2 patients receiving placebo and in 3 patients receiving any dose level of upadacitinib. One patient in the 7.5 mg once-daily upadacitinib arm developed malignant melanoma, and no venous thromboembolic events or deaths were reported.

### Reference

1. Sandborn WJ, Ghosh S, Panés J, et al. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately to severely active ulcerative colitis: data from the phase 2b study U-ACHIEVE [UEG Week abstract OP195]. *United European Gastroenterol J*. 2018;6(suppl 1).

**Table 2.** Efficacy Results at Week 8

Endpoint	Upadacitinib				Placebo (n=46)
	7.5 mg Once Daily (n=47)	15 mg Once Daily (n=49)	30 mg Once Daily (n=52)	45 mg Once Daily (n=56)	
Clinical remission (per adapted Mayo score) <sup>a</sup>	8.5%	14.3% ( $P < .05$ )	13.5% ( $P < .05$ )	19.6% ( $P < .01$ )	0%
Endoscopic improvement <sup>b</sup>	14.9% ( $P < .05$ )	30.6% ( $P < .001$ )	26.9% ( $P < .001$ )	35.7% ( $P < .001$ )	2.2%
Clinical remission (per full Mayo score) <sup>c</sup>	8.5%	10.2% ( $P < .05$ )	11.5% ( $P < .05$ )	19.6% ( $P < .01$ )	0%
Clinical response (per adapted Mayo score) <sup>d</sup>	29.8% ( $P < .05$ )	44.9% ( $P < .001$ )	44.2% ( $P < .001$ )	50.0% ( $P < .001$ )	13.0%

<sup>a</sup>Clinical remission (adapted Mayo score [Mayo score without physician global assessment]) is defined as a stool frequency subscore  $\leq 1$ , rectal bleeding subscore (RBS) = 0, and endoscopic subscore (ES)  $\leq 1$ . <sup>b</sup>Endoscopic improvement is defined as ES  $\leq 1$ . <sup>c</sup>Clinical remission (per full Mayo score) is defined as a full Mayo score  $\leq 2$  with no subscore  $> 1$ . <sup>d</sup>Clinical response (per adapted Mayo score) is defined as a decrease from baseline in the adapted Mayo score  $\geq 2$  points and  $\geq 30\%$  from baseline, plus a decrease in RBS  $\geq 1$  or an absolute RBS  $\leq 1$ .

Adapted from Sandborn WJ et al. UEG Week abstract OP195. *United European Gastroenterol J*. 2018;6(suppl 1).

# Highlights in IBD From the American College of Gastroenterology 2018 Annual Scientific Meeting and United European Gastroenterology Week 2018: Commentary

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We are making terrific progress in advancing our care for inflammatory bowel disease (IBD) patients, with emphasis on optimization of existing therapies, understanding of which patients should be treated with specific therapies and at what time, and exploration of novel mechanisms of action with favorable efficacy and safety profiles. There were a number of important and exciting presentations on IBD at this year's American College of Gastroenterology (ACG) Annual Scientific Meeting, which was held in Philadelphia, Pennsylvania, and United European Gastroenterology (UEG) Week, which was held in Vienna, Austria. Noteworthy research involved the definition of early disease as well as new data on various treatment options, including vedolizumab, ustekinumab, different Janus kinase (JAK) inhibitors, and other therapies in development such as etrasimod and risankizumab.

## Defining Early Disease

A poster by Dr Laurent Peyrin-Biroulet and colleagues at UEG Week 2018 featured findings of a systematic literature review on the definition of early disease in IBD.<sup>1</sup> This is an important issue because of the generally accepted principle in IBD management (especially Crohn's disease) that the earlier patients are treated, the more likely they are to respond to therapy, and

the more likely they are to continue to respond over time. This comprehensive literature review, which included 124 studies, demonstrated that what is called early disease varies quite widely by study. However, the most common definition and cutoff for early disease in these studies has been less than 3 months for ulcerative colitis and between 3 and 6 months for Crohn's disease. This is likely because the time between disease onset and diagnosis in ulcerative colitis tends to be shorter than in Crohn's disease because patients who have active urgency and rectal bleeding come to medical attention and are diagnosed more quickly than patients with Crohn's disease, who may have subclinical small bowel disease for years prior to appropriate diagnosis.

It is crucial to recognize in studies of natural history, risk factors, and response to therapy the distinction between symptom onset and disease diagnosis and, furthermore, to understand the importance of giving patients appropriate therapies earlier in their disease course. Therefore, it is helpful to look at this comprehensive analysis and to work toward having a better definition of disease onset and what early disease means as we discuss positioning therapies earlier.

## Vedolizumab

Vedolizumab was approved in the United States and subsequently in

Europe for the treatment of moderate to severe Crohn's disease and moderate to severe ulcerative colitis in 2014. The drug works by inhibiting  $\alpha 4\beta 7$  integrins known as mucosal vascular addressin cell adhesion molecules, which target the mucosal immune system. Because vedolizumab is selective to the mucosal immune system, it has a favorable safety profile and a lack of reported systemic toxicity. Now that the drug has been on the market for almost 5 years, a number of studies have characterized how it is being used and what we can learn from real-world experiences. Several such abstracts were presented at the ACG 2018 meeting and UEG Week 2018.

## Real-World Experiences

At the ACG 2018 meeting, a poster by Dr Jenna L. Koliani-Pace and colleagues reported on the shift from the early days of this therapy to its more current use.<sup>2</sup> When vedolizumab first became available, as is common with new therapies, it was positioned to be used after patients had already failed anti-tumor necrosis factor (TNF) therapies and had been refractory to other treatment. More recently, however, vedolizumab is being used as a first-line biologic option or earlier in the disease course and treatment algorithm. Dr Koliani-Pace and colleagues reviewed the Truven MarketScan Database, which is a large administrative claims database, and data from the multicenter

VICTORY Consortium, and found that as patients received vedolizumab earlier, they had better outcomes and were more likely to respond to treatment. These findings are similar to what we have seen with all modern therapies in IBD, namely that earlier use is more effective. Thus, it is important to further understand which patients can be treated with vedolizumab because giving them the drug earlier is beneficial.

This theme is supported by several other real-world analyses presented this year. For example, at UEG Week 2018, there were 2 separate posters that described the German experience with vedolizumab in Crohn's disease and ulcerative colitis.<sup>3,4</sup> Both of these studies demonstrated findings consistent with clinical trial results. The results of vedolizumab as a first-line biologic therapy in Crohn's disease and ulcerative colitis were found to be similar to patients who received an anti-TNF agent as their first biologic, and the results were also similar to patients who received vedolizumab as their second-line biologic or when patients received an anti-TNF agent after a prior anti-TNF agent.<sup>5,6</sup> The message is consistent that the first drug used has the best results and that when vedolizumab is used earlier, there is a greater likelihood of the patient responding.

### ***Use of Magnetic Resonance Enterography***

Also presented at UEG Week 2018 were results of the VERSIFY study.<sup>7</sup> This prospective study examined the use of magnetic resonance (MR) enterography and endoscopy to explore measures of mucosal healing in patients who received vedolizumab for Crohn's disease. This study found that treatment with vedolizumab over 26 weeks was associated with reduced MR enterography disease severity (as measured by the Magnetic Resonance Index of Activity score), which progressed out to 52 weeks, suggesting that the benefit for healing continues to improve over time.

In addition, MR enterography may provide additional information that endoscopy alone does not. The correlation between MR enterography and endoscopic examinations was only moderate, suggesting that improvement in full-thickness disease activity may provide important additional information in Crohn's disease. The utility and cost-effectiveness of serial MR enterography examinations in the United States have not been fully described yet, but the additional information of such examinations is certainly important. I was pleased to see results from this important study, which suggest how we might soon use cross-sectional imaging in patients with Crohn's disease to assess treatment response and better understand mucosal healing to achieve deep remission.

### ***Vedolizumab Subcutaneous***

Also important were the results from the VISIBLE 1 phase 3 trial presented by Dr William J. Sandborn at UEG Week 2018.<sup>8</sup> This trial examined the use of a new vedolizumab formulation (vedolizumab subcutaneous [SC]) in patients with moderate to severe ulcerative colitis. Patients were randomized to receive 2 intravenous (IV) loading doses of vedolizumab and then underwent randomization to ongoing IV or SC vedolizumab or placebo: either vedolizumab SC 108 mg every 2 weeks plus placebo IV every 8 weeks; vedolizumab IV 300 mg every 8 weeks plus placebo SC every 2 weeks; or placebo SC and IV.

This study demonstrated that SC dosing after IV loading was similar in its effect in achieving clinical remission, mucosal healing, and durable clinical response at week 52, as well as durable clinical remission and corticosteroid-free clinical remission. In other words, the SC formulation of vedolizumab had equal efficacy to what is well known about the IV maintenance dosing of vedolizumab. The safety profile was the same. Ten percent of patients had injection site reactions, which did not limit treatment. Thus, vedolizumab SC will be a

nice option for patients to know that they can have the safety and efficacy of vedolizumab in ulcerative colitis along with the added convenience of being able to dose the treatment themselves.

### **Ustekinumab**

At the ACG 2018 meeting, Dr Bruce E. Sands presented results from the phase 3 UNIFI study, which introduced a new mechanism of action in the management of moderate to severe ulcerative colitis for a drug with which we are already familiar.<sup>9</sup> Ustekinumab, a monoclonal antibody targeting the shared p40 subunit of cytokines interleukin (IL)-12 and -23, has been part of our armamentarium since it was approved for the treatment of moderate to severe Crohn's disease in 2016. The UNIFI study demonstrated the superiority of ustekinumab at a weight-based loading IV dose followed by maintenance SC dose (90 mg) every 8 weeks compared with placebo for achieving the primary endpoint of clinical remission as well as for providing a benefit in achieving mucosal healing. The overall benefit of this therapy was not large, but it is important to note that many of the patients included in this trial had previously been exposed to biologic agents and, thus, may have represented a more resistant disease state.

Dr Sands also presented results of another study on ustekinumab at the ACG 2018 meeting, this one on the long-term efficacy of the drug with and without concomitant immunosuppressants in Crohn's disease patients.<sup>10</sup> These results were from 2 years of the long-term extension of IM-UNITI, the maintenance ustekinumab trial in Crohn's disease. The findings demonstrated that the presence of an immunomodulator in combination with ustekinumab did not improve the likelihood of responding to the therapy or the likelihood of maintaining remission over time.

In addition, it was interesting to see that the use of a concomitant immunomodulator did not change

the pharmacokinetics of ustekinumab. This is in contrast to the well-described observation that concomitant immunomodulators raise serum levels of anti-TNF therapies (independent of preventing immunogenicity). This new finding in combination with the phase 3 trial results demonstrating a very low immunogenicity rate with ustekinumab suggest that this therapy may be used effectively as a monotherapy in patients.<sup>11</sup>

## Janus Kinase Inhibitors

### *Tofacitinib*

The ACG 2018 meeting included an oral presentation by Dr Gary R. Lichtenstein on a long-term extension follow-up of tofacitinib in the setting of ulcerative colitis.<sup>12</sup> Tofacitinib was the first JAK inhibitor available in IBD, inhibits JAK-1 and -3 and a bit of JAK-2, and was approved this year for the treatment of moderate to severe ulcerative colitis. In the open-label extension study, patients received either 5 or 10 mg of tofacitinib twice daily, and it was notable that the safety profile was stable. This finding matches previous research on the drug, and adverse events did not increase the longer patients received therapy.<sup>13</sup>

In addition, the results for remission, mucosal healing, and clinical response demonstrated that tofacitinib therapy was stable over time in most patients, providing reassurance to ulcerative colitis patients who are using this therapy now that it has stable efficacy and that there are not any additional safety signals. These findings are also consistent with what has been seen in the rheumatoid arthritis experience, where the drug has been on the market longer than it has been for ulcerative colitis.

Another message from the extension study is that although we know that JAK inhibition appears to increase cholesterol levels, there has not been an increase in cardiovascular events.<sup>13</sup> This may be because JAK inhibition also may prevent atherosclerosis.

### *Upadacitinib*

Upadacitinib inhibits only JAK-1 and, thus, is a more selective JAK inhibitor than tofacitinib. At UEG Week 2018, Dr Sandborn presented results from the phase 2b U-ACHIEVE study on upadacitinib in patients with moderate to severe ulcerative colitis.<sup>14</sup> Upadacitinib demonstrated efficacy superior to placebo with a dose response in which the 45-mg once-daily dose appeared to have the highest clinical remission rate compared with the smaller doses. In addition, a dose response was seen in endoscopic improvement and in clinical remission using the full Mayo score. Thus, overall, upadacitinib is a favorable, selective JAK inhibitor that we expect will move forward as another oral option in small molecules for the treatment of ulcerative colitis. Selective JAK-1 inhibition is also being actively studied in Crohn's disease.

### *TD-1473*

Study results of another JAK inhibitor, TD-1473, were also presented at UEG Week 2018.<sup>15</sup> This intestinally restricted pan-JAK inhibitor does not have the systemic effect of the other JAK inhibitors that have been studied. In a phase 1b study of moderate to severe ulcerative colitis patients, the agent was administered in a range of doses and was well tolerated over the duration of the study (4 weeks). It is likely that an intestinally restricted JAK inhibitor would have a lower risk of developing infectious complications than that seen with systemic immunosuppressive therapies.

## Other Therapies in Development

### *Etrasimod*

At the ACG 2018 meeting, Dr Sandborn presented results of the OASIS study, a randomized, double-blind, placebo-controlled, phase 2 trial of the sphingosine 1 phosphate receptor modulator etrasimod.<sup>16</sup> This drug has a mechanism of action that is novel to ulcerative colitis. Other therapies in this class are also under investigation,

but none are currently available for clinical practice. Etrasimod's mechanism of action is thought to involve the prevention of lymphocytes from migrating out of lymph nodes; the lymphocytes are, therefore, restricted from reaching the bowel because they are trapped in the lymph nodes.

In the OASIS study, etrasimod was demonstrated to be superior to placebo, and the study results support moving the drug into phase 3 investigation. A dose-response relationship was observed and, as has been seen with other therapies such as azathioprine and 5-aminosalicylic acid, this therapy worked quite rapidly, with a decrease in rectal bleeding as early as 2 weeks. Interestingly, fewer patients had serious adverse events with etrasimod than with placebo, presumably because the placebo patients experienced worsening of their colitis and had other complications. If this drug demonstrates similar findings in phase 3, it looks to be a safe oral treatment option for ulcerative colitis.

### *Risankizumab*

Interim results of an extension of an ongoing phase 2 study on risankizumab were presented by Dr Marc Ferrante at UEG Week 2018.<sup>17</sup> Risankizumab is a p19 inhibitor and, thus, is more selective for IL-23 than ustekinumab. In this phase 2 study and open-label extension, risankizumab has demonstrated good efficacy with sustained clinical and endoscopic remission in difficult-to-treat moderate to severe Crohn's disease, along with a favorable safety profile, not unlike ustekinumab.

**Disclosure:** In the past 12 months, Dr Rubin has served as a consultant to AbbVie, AbGenomics, Allergan, Arena Pharmaceuticals, Biomica, Ferring Pharmaceuticals, Genentech/Roche, Janssen Pharmaceuticals, Lilly, Medtronic, Merck & Co, Napo Pharmaceuticals, Pfizer, Shire, Takeda, and Target PharmaSolutions. He has also received grant support from AbbVie, Genentech/Roche, Janssen Pharmaceuticals, Prometheus Laboratories, Shire, and Takeda.

## References

1. Peyrin-Biroulet L, Jairath V, Wright D, Demuth D, Campbell-Hill S, Dulai PS. Defining 'early disease' in inflammatory bowel disease: the results of a systematic literature review [UEG Week abstract P0351]. *United European Gastroenterol J*. 2018;6(suppl 1).
2. Koliiani-Pace JL, Singh S, Hirten R, et al. Shifts in vedolizumab utilization across the United States are associated with improved outcomes [ACG abstract P0444]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.
3. Helwig U, Mross M, Schubert S, et al. Real-world effectiveness of vedolizumab and anti-tumour necrosis factor alpha treatment over 6 months in ulcerative colitis patients: a German retrospective chart review [UEG Week abstract P1002]. *United European Gastroenterol J*. 2018;6(suppl 1).
4. Helwig U, Mross M, Schubert S, et al. Real-world effectiveness of vedolizumab and anti-tumour necrosis factor alpha treatment over 6 months in Crohn's disease patients: a German retrospective chart review [UEG Week abstract P1589]. *United European Gastroenterol J*. 2018;6(suppl 1).
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. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66(5):839-851.
7. Rimola J, Danese S, Feagan B, et al. Magnetic resonance enterography assessment of mucosal healing with vedolizumab in patients with moderately to severely active Crohn's disease: results from the VERSIFY study [UEG Week abstract OP175]. *United European Gastroenterol J*. 2018;6(suppl 1).
8. Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of a new vedolizumab subcutaneous formulation for ulcerative colitis: results of the VISIBLE 1 phase 3 trial [UEG Week abstract LB03]. *United European Gastroenterol J*. 2018;6(suppl 1).
9. Sands BE, Sandborn WJ, Panaccione R, et al. Safety and efficacy of ustekinumab induction therapy in patients with moderate to severe ulcerative colitis: results from the phase 3 UNIFI study [ACG abstract 54A]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.
10. Sands BE, Kramer BC, Gasink C, et al. Long-term efficacy and safety of ustekinumab with and without concomitant immunosuppressants for Crohn's disease: results from IM-UNITI long-term extension through two years [ACG abstract 49]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.
11. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI-IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375(20):1946-1960.
12. Lichtenstein GR, Loftus EV, Bloom S, 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 4.9 years of treatment [ACG abstract 13]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.
13. Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736.
14. Sandborn WJ, Ghosh S, Panés J, et al. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately to severely active ulcerative colitis: data from the phase 2b study U-ACHIEVE [UEG Week abstract OP195]. *United European Gastroenterol J*. 2018;6(suppl 1).
15. Sandborn WJ, Bhandari R, Leighton J, et al. The intestinally restricted, orally administered, pan-JAK inhibitor TD-1473 demonstrates favorable safety, tolerability, pharmacokinetics, and signal for clinical activity in subjects with moderately to severely active ulcerative colitis [UEG Week abstract LB05]. *United European Gastroenterol J*. 2018;6(suppl 1).
16. Sandborn WJ, Peyrin-Biroulet L, Trokan L, et al. A randomized, double-blind, placebo-controlled trial of a selective oral sphingosine 1 phosphate receptor modulator etrasimod in moderate to severe ulcerative colitis: results from the OASIS study [ACG abstract 11]. Presented at the American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.
17. Ferrante M, Panés J, Baert F, et al. Long-term safety and efficacy of risankizumab treatment in patients with Crohn's disease: interim results of the ongoing phase 2 open-label extension study [UEG Week abstract OP307]. *United European Gastroenterol J*. 2018;6(suppl 1).



