THE GI PERSPECTIVE

ISSUE 1

CURRENT TOPICS IN UC: THE VARSITY TRIAL

FEATURING
DR. STEPHEN HANAUER

"The VARSITY study is the first ever prospective, randomized head-to-head trial of biologics in ulcerative colitis."

INSIDE THIS ISSUE:

- The current and future impact of head-to-head trials in ulcerative colitis (UC) clinical practice
- Data overview of the VARSITY trial

Dr. Hanauer is a paid consultant of Takeda Pharmaceuticals, Inc.

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"For the physician and patient discussing their treatment options, comparative evidence is incredibly powerful information."

DR. STEPHEN HANAUER

- Professor of Medicine, Northwestern University Feinberg School of Medicine
- Medical Director, Digestive Health Center Northwestern Medicine, Chicago, IL
- Internationally recognized expert in the treatment of inflammatory bowel disease (IBD)

HEAD-TO-HEAD CLINICAL TRIALS IN UC

Including a closer look at the **VARSITY trial** with **Dr. Stephen Hanauer**

ENTYVIO (vedolizumab) is for 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.

Q: *What are the major advancements in UC over the past 10 years?*

The landscape for treating UC has changed dramatically over the past few years. The early adoption of a treat to target approach and the approval of more targeted therapies are 2 major advancements.[1,2] The challenge, however, is that gastroenterologists have very limited clinical data to help inform their decision-making around the differences between these therapies.

Q: *What are the advantages of head-to-head trials to practicing gastroenterologists?*

As both a researcher and a clinician, it is difficult to interpret noncomparative studies due to numerous variables, including time frame of studies (biologics over 2 decades), patient demographics, methodologies, and end points that impact trial outcomes. Head-to-head trials are very important, as they convert hypotheses into more interpretive conclusions, allowing physicians to make more informed decisions.[3]

Q: *How would you describe the VARSITY trial?*

The VARSITY trial is the largest comparative effectiveness study of biologics to date in UC.[4,5] This was a head-to-head trial that included a "treat-through design," rather than rerandomizing induction "responders" into maintenance therapy, and focused on 3 key end points: clinical remission, endoscopic improvement of mucosa, and steroid-free remission.

UC=ulcerative colitis.

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.

Please see additional Important Safety Information on page 11.

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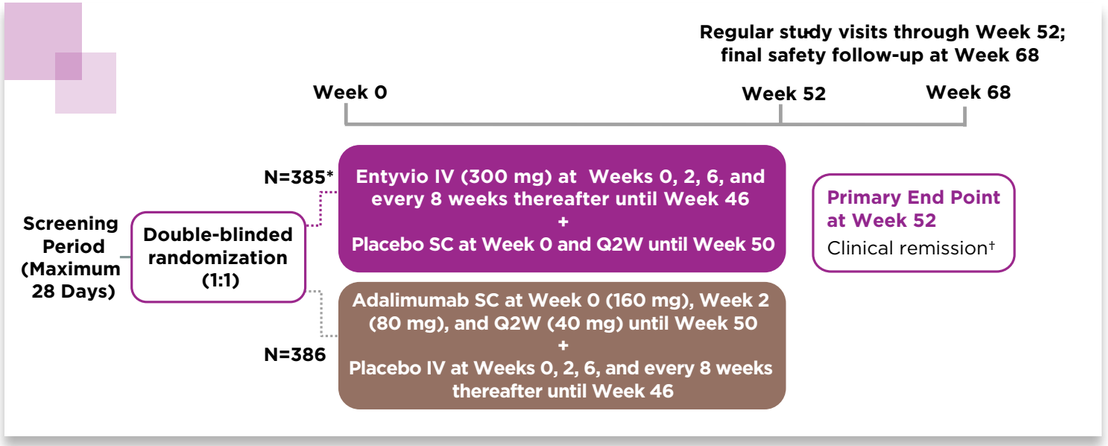
VARSITY: THE FIRST HEAD-TO-HEAD STUDY OF BIOLOGIC THERAPIES IN UC[4,5]

- VARSITY is a phase 3b randomized, double-blind, double-dummy, multicenter, active-controlled superiority trial that enrolled a total of 771 patients[4,5]



Study Details[4-6]

- Eligible patients were adults (aged 18 to 85 years) with moderately to severely active UC, defined as a complete Mayo score of 6 to 12 (range 0 to 12; higher scores represent more active disease), an endoscopic subscore of ≥2, colonic involvement of ≥15 cm, and confirmed diagnosis of UC for ≥3 months. TNFα inhibitor-naïve patients who had not responded or lost response to conventional treatments were eligible. Centrally read endoscopies were performed at Weeks 14 and 52
- Dosing was consistent with the US product label for both Entyvio and adalimumab; no dose escalation was permitted for either treatment group
- After induction, patients remained in their respective treatment group throughout the maintenance phase (treat-through design)
- Enrollment, capped at 25% (~21% was reached), included patients who discontinued treatment with a TNFα inhibitor (except adalimumab) due to documented reasons other than safety. The majority of the trial population (97.3%) had moderately to severely active disease (Mayo score 6-12). Patients with mild disease represented significant protocol deviations. Per-protocol sensitivity analyses indicated no change from overall population results
- Population was stratified by prior TNFα inhibitor treatment and concomitant use of oral corticosteroids
- Patients naïve to TNFα inhibitor therapy were enrolled if they were failing current treatment (eg, CS, 5-ASA, or immunomodulators). Per-protocol sensitivity analyses indicated no change from overall population results. Patients on a 5-ASA or immunomodulator at baseline maintained stable doses throughout the study

*Includes 2 patients who were randomized but did not receive a dose of Entyvio. †Clinical remission was defined as a total score ≤2 on the Mayo scale with no subscore >1 on any of the 4 components.

5-ASA=5-aminosalicylate; CS=corticosteroid; IV=intravenous; Q2W=every 2 weeks; SC=subcutaneous; TNFα=tumor necrosis factor alpha; UC=ulcerative colitis.

***Q:** What are the most compelling aspects of the VARSITY trial design?*

The VARSITY study is the first ever prospective, randomized head-to-head trial of biologics in ulcerative colitis. That in and of itself is a bold accomplishment.[4,5]

VARSITY BASELINE PATIENT CHARACTERISTICS[4]

Characteristic	Adalimumab N=386	Entyvio N=385
Age – yr (mean ± SD)	40.5 ± 13.4	40.8 ± 13.7
Male sex – n (%)	216 (56.0)	234 (60.8)
White race – n (%)*	341 (88.3)	345 (89.6)
Body weight – kg (mean ± SD)	73.4 ± 18.4	72.7 ± 17.0
Current smoker – n (%)†	23 (6.0)	19 (4.9)
Duration of UC – yr (mean ± SD)‡	6.4 ± 6.0	7.3 ± 7.2
Total score on the Mayo scale (mean ± SD)§	8.7 ± 1.5	8.7 ± 1.6
Fecal calprotectin – ug/g (mean ± SD)¶	2771 ± 4064	2929 ± 5920
Previous treatment with an anti-TNFα therapy with documented reason for discontinuation – n (%)	81 (21.0)	80 (20.8)
Previous treatment with an anti-TNFα therapy with documented failure – n (%)	79 (20.5)	72 (18.7)
Inadequate response	40 (50.6)	36 (50.0)
Loss of response	29 (36.7)	24 (33.3)
Side effects	3 (3.8)	7 (9.7)
Missing data	7 (8.9)	5 (6.9)
Concomitant medications for UC – n (%)		
Corticosteroids only‖	140 (36.3)	139 (36.1)
Immunomodulators only**	100 (25.9)	101 (26.2)

*Race was reported by the patient. †Data on smoking status were missing for 2 patients in the Entyvio group. ‡1 patient in the adalimumab group had UC of unknown duration. §The total score on the Mayo scale ranges from 0 to 12, with higher scores indicating more active disease; subcomponents: stool frequency, rectal bleeding, endoscopy (sigmoidoscopy), physician's global assessment. Total Mayo scores were available for 384 patients in the adalimumab group and 380 patients in the Entyvio group. ¶Data on fecal calprotectin were available for 332 patients in the adalimumab group and 341 patients in the Entyvio group. ‖As reported in the interactive web response system. **As reported in the electronic case-report form. The commonly used immunomodulators in order of greatest to least were azathioprine, mercaptopurine, and methotrexate.

SD=standard deviation; TNFα=tumor necrosis factor alpha; UC=ulcerative colitis; yr=year.

Important Safety Information

- Infusion-related reactions and hypersensitivity reactions including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have been reported. These reactions may occur with the first or subsequent infusions and may vary in their time of onset from during infusion or up to several hours post-infusion. If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.

Please see additional Important Safety Information on page 11.

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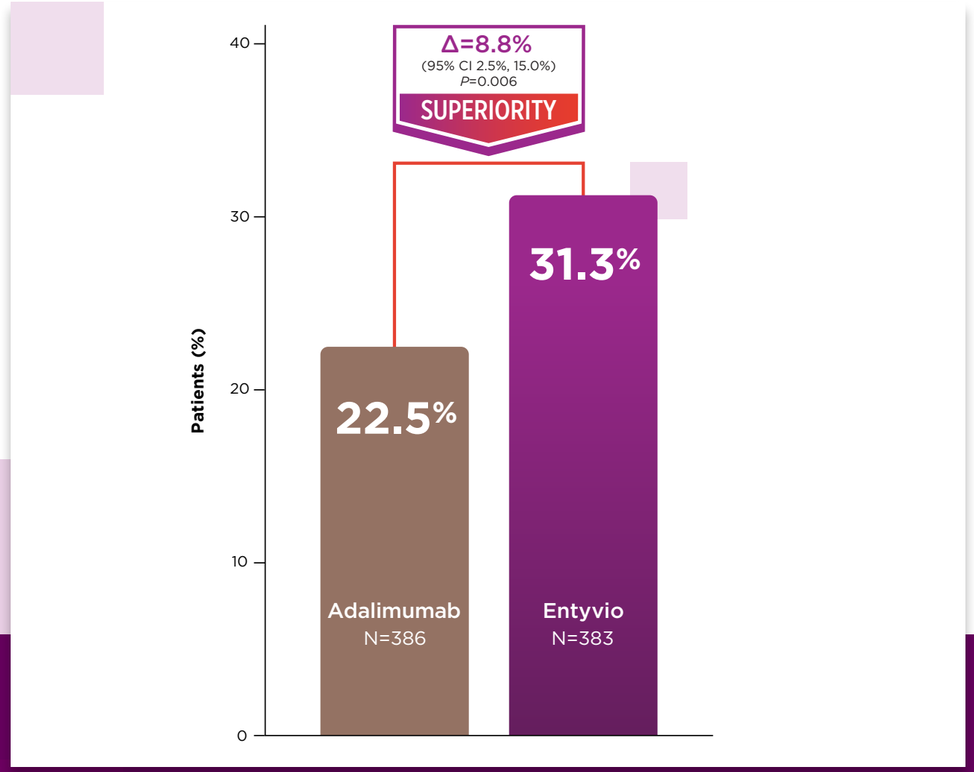
ENTYVIO (VEDOLIZUMAB) ACHIEVED SUPERIOR CLINICAL REMISSION VS ADALIMUMAB AT WEEK 52 IN THE OVERALL POPULATION[4]

Primary End Point: Clinical Remission* at Week 52 in the Overall Population[4†]



For me, the most compelling aspect of the VARSITY trial is that it demonstrated the superiority of vedolizumab to adalimumab in achieving clinical remission at 52 weeks.

*Clinical remission was defined as a total score ≤2 on the Mayo scale with no subscore >1 on any of the 4 components. †Full analysis set includes all randomized patients who received at least 1 dose of study drug.

CI=confidence interval.

Important Safety Information

- 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.

Please see additional Important Safety Information on page 11.

SAFETY WAS EVALUATED IN 383 PATIENTS: NO NEW SAFETY SIGNALS WERE OBSERVED FOR ENTYVIO[4,5,7]

- Study was not designed to assess safety differences[5]

Event[4†]	Adalimumab N=386*	Entyvio N=383*
	Patients, n (%)	
Any adverse events	267 (69.2)	240 (62.7)
Mild	118 (30.6)	111 (29.0)
Moderate	109 (28.2)	92 (24.0)
Severe	40 (10.4)	37 (9.7)
Leading to study drug discontinuation	25 (6.5)	17 (4.4)
Adverse events (excluding UC)	250 (64.8)	229 (59.8)
Serious adverse events‡	53 (13.7)	42 (11.0)
Serious adverse events that led to a discontinuation of a trial drug	13 (3.4)	10 (2.6)
Serious adverse events (excluding UC)	27 (7.0)	28 (7.3)
Deaths§	0	1 (0.3)
Exposure-adjusted incidence rates of adverse events¶	**Number of patients/incidence rates per 100 patient-years**	
Infections and infestations	124/34.6	103/23.4
Clostridia	2/0.6	5/1.1
Herpes virus	15/4.2	2/0.5
Lower respiratory tract	7/2.0	5/1.1
Upper respiratory tract	65/18.1	55/12.5
Serious infections and infestations	8/2.2	7/1.6
Musculoskeletal and connective tissue disorders	44/12.3	50/11.4
Arthralgia	16/4.5	18/4.1
Skin and subcutaneous tissue disorders	52/14.5	38/8.6
Psoriasis	6/1.7	1/0.2

Adverse Events in the Safety Population[6]

- The most frequent AEs* reported for adalimumab and Entyvio were as follows: ≥1 TEAE, 35.8% and 32.9%; ulcerative colitis, 16.3% and 11.5%; nasopharyngitis, 7.8% and 7.0%; headache, 5.4% and 7.0%; anemia, 6.7% and 5.2%; abdominal pain, 5.2% and 4.7%; upper respiratory tract infection, 4.4% and 5.2%

*Adverse events were classified according to the *Medical Dictionary for Regulatory Activities* System Organ Class categorization and preferred terms (version 21.0). The safety population was defined as all patients who received at least one dose of the study drug. †Adverse events that occurred during the trial period. Trial period was the time from the first dose of a trial drug and up to 126 days after the last dose. ‡No cases of progressive multifocal leukoencephalopathy. §The 1 death in the Entyvio group was not considered by the site investigator to be related to the trial drug. ¶The exposure-adjusted incidence rate (per 100 patient-years) was defined as the number of patients who had the adverse event divided by the total exposure time among the patients. The results included the final 68-week safety follow-up.

AE=adverse event; TEAE=treatment-emergent adverse event; UC=ulcerative colitis.

Important Safety Information

- Progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported in the post marketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm^3 and prior and concomitant immunosuppression). Although unlikely, 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.

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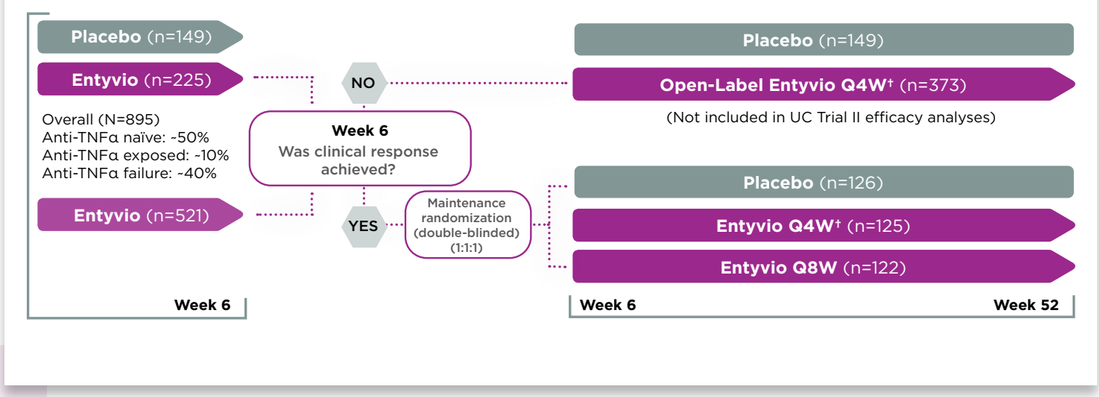
Please see additional Important Safety Information on page 11.

ENTYVIO UC TRIALS I AND II STUDY DESIGN[5,7,8]

- UC Trial I: 2 cohorts with primary end point evaluation at Week 6*
  - —Cohort 1—Blinded: Randomized 3:2 to receive 300 mg Entyvio or placebo intravenously at Weeks 0 and 2
  - —Cohort 2—Open-Label: 300 mg Entyvio intravenously at Weeks 0 and 2 (not included in UC Trial I efficacy analyses)
- UC Trial II: Patients receiving Entyvio in cohorts 1 and 2 of UC Trial I who achieved clinical response at Week 6 were randomly assigned to continue receiving Entyvio every 4 or 8 weeks, or placebo every 4 weeks for up to 52 weeks*



Week 6 Primary End Point[8] Clinical response

Week 52 Primary End Point[8] Clinical remission

*UC Trials I and II were randomized, double-blind, placebo-controlled studies that enrolled adult patients with moderately to severely active UC who had failed at least 1 conventional therapy, including corticosteroids or immunomodulators and/or ≥1 anti-TNFα therapy. Concomitant aminosalicylates, corticosteroids, and immunomodulators were permitted. Corticosteroids were tapered after Week 6; in the United States, immunosuppressants were discontinued after Week 6. †The Entyvio Q4W dosing regimen did not demonstrate additional clinical benefit over the Q8W dosing regimen. The Q4W dosing regimen is not the recommended dosing regimen.

Q4W=every 4 weeks; Q8W=every 8 weeks; TNFα=tumor necrosis factor alpha; UC=ulcerative colitis.

Important Safety Information

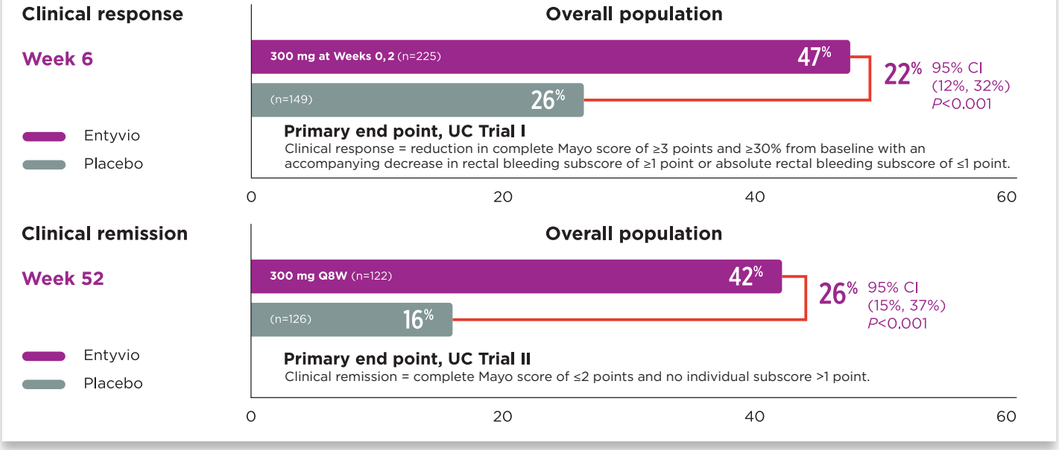
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

Please see additional Important Safety Information on page 11.

DATA FROM ENTYVIO (VEDOLIZUMAB) PRESCRIBING INFORMATION

RESULTS: PRIMARY END POINTS OF UC TRIALS I AND II[7]

Clinical Response at Week 6 and Clinical Remission at Week 52



SAFETY EVALUATED IN CLINICAL TRIALS — UC I AND II AND CD I AND III[7]

Trials included more than 800 patients who received Entyvio for more than 2 years

- Infection rates with Entyvio were 0.85 per patient-year vs 0.7 for placebo
  - —Infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection
  - —2% of patients discontinued Entyvio due to infections
- Serious infection rates with Entyvio were 0.07 per patient-year vs 0.06 for placebo
  - —Serious infections included anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis
- Adverse reactions were reported in 52% of patients treated with Entyvio (N=1434) and 45% of patients treated with placebo (N=297)
  - —Over 52 weeks, 7% of patients treated with Entyvio experienced serious adverse reactions compared to 4% treated with placebo
- Although unlikely, a risk of PML cannot be ruled out:
  - —PML, a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised
  - —1 case of PML in an Entyvio-treated patient with multiple contributory factors has been reported in the postmarketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm^3 and prior and concomitant immunosuppression)
- Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities

CD=Crohn's disease; CI=confidence interval; PML=progressive multifocal leukoencephalopathy; UC=ulcerative colitis.

Important Safety Information

- 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.

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Please see additional Important Safety Information on page 11.

INDICATIONS: ENTYVIO (VEDOLIZUMAB)

Adult Ulcerative Colitis (UC)

ENTYVIO (vedolizumab) is indicated in adults for the treatment of moderately to severely active UC.

Adult Crohn’s Disease (CD)

ENTYVIO (vedolizumab) is indicated in adults for the treatment of moderately to severely active CD.

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, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have been reported. These reactions may occur with the first or subsequent infusions and may vary in their time of onset from during infusion or up to several hours post-infusion. If anaphylaxis or other serious infusion-related or hypersensitivity 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.
- Progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported in the post marketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm^3 and prior and concomitant immunosuppression). Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.
- Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see accompanying ENTYVIO (vedolizumab) full **Prescribing Information**, including **Medication Guide**.

Entyvio® vedolizumab

Entyvio is indicated for adults with moderately to severely active UC for whom other therapies have not worked well enough or cannot be tolerated.

> *Entyvio is a good option as a first-line biologic in UC. It has an established safety profile and has been proven to be effective over the long term. Why not consider this gut-selective treatment option?*

DR. STEPHEN HANAUER

Entyvio Mechanism of Action[7]

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

GI=gastrointestinal; MAdCAM-1=mucosal vascular addressin cell adhesion molecule-1; UC=ulcerative colitis.

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.

Please see additional Important Safety Information on page 11.

References: 1. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. *Am J Gastroenterol*. 2019:114(6):874-883. **2.** D'Haens G, Daperno M. *Curr Gastroenterol Rep*. 2006;8(6):506-512. **3.** Peyrin-Biroulet L, Lopez A, Sandborn W. *J Crohns Colitis*. 2017:11(suppl 2):S567-S575. **4.** Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. *N Engl J Med*. 2019;381(13):1215-1226. **5.** Data on File. Takeda Pharmaceuticals. **6.** Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. *N Engl J Med*. 2019;381(13):1215-1226. (supplemental appendix). **7.** Entyvio (vedolizumab) prescribing information. Takeda Pharmaceuticals. **8.** Feagan BG, Rutgeerts P, Sands BE, et al. *N Engl J Med*. 2013;369(8):699-710.

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