THE GI PERSPECTIVE

ISSUE 1

CURRENT TOPICS IN UC:

THE VARSITY TRIAL

FEATURING

Dr. Stephen Hanauer

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

> **“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

Takeda

> 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, Illinois
- Internationally recognized expert in the treatment of inflammatory bowel disease (IBD)

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HEAD-TO-HEAD CLINICAL TRIALS IN UC

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

ENTYVIO: A biologic for the treatment of adults with moderately to severely active ulcerative colitis (UC).

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. The challenge, however, is that gastroenterologists have very limited clinical data to help inform their decision-making around the differences among these therapies.

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.

How would you describe the VARSITY trial?

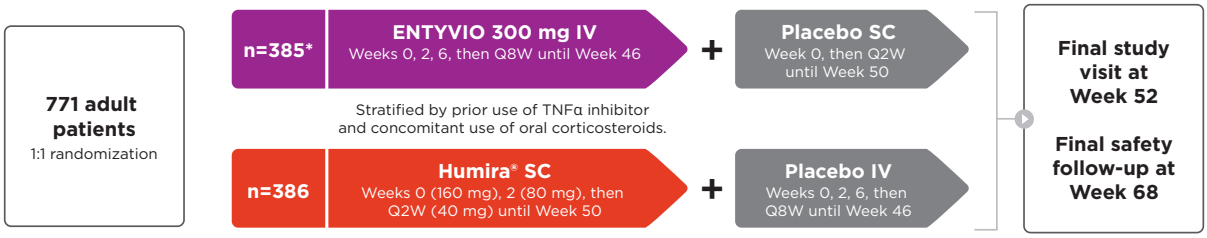
The VARSITY trial was the first comparative effectiveness study of biologics in UC. This was a head-to-head trial that included a "treat-through design," rather than rerandomizing induction "responders" into maintenance therapy, and focused on 3 key end points: clinical remission, endoscopic improvement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

VARSITY

The first head-to-head study of biologics in moderate to severe UC[1,2]

STUDY DESIGN[1,3,4]

VARSITY was a double-blind, double-dummy, active-controlled trial that compared ENTYVIO with Humira® (adalimumab) in adults with moderately to severely active UC.[1]



Humira® (AbbVie Inc., North Chicago, IL). For information related to Humira, please see AbbVie.com.

Study Details[1,3,4]

- Eligible patients were adults (aged 18 to 85 years) with moderately to severely active ulcerative colitis, 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 a confirmed diagnosis of ulcerative colitis for ≥3 months. Anti-TNFα-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 Humira®; no dose escalation was permitted for either treatment group. After induction, patients stayed in their treatment group throughout the maintenance phase (treat-through design)
- Enrollment of patients who discontinued treatment with an anti-TNFα (except adalimumab) due to documented reasons other than safety was capped at 25% (~21% was reached). Most 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
- Patients naïve to anti-TNFα 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

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."**

*Includes 2 patients who were randomized but never received any study drug.

CS=corticosteroids; IV=intravenous; Q2W=every 2 weeks; Q8W=every 8 weeks; SC=subcutaneous; TNFα=tumor necrosis factor alpha; 5-ASA=5-aminosalicylate.

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VARSITY

The first head-to-head study of biologics in moderate to severe UC[1,2]

BASELINE CHARACTERISTICS OF OVERALL STUDY POPULATION[1]

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

*Data on smoking status were missing for 2 patients in the ENTYVIO group.
†One patient in the Humira® group had ulcerative colitis of unknown duration.
‡Scores were available for 384 patients in the Humira® group and 380 patients in the ENTYVIO group.
§Data on fecal calprotectin were available for 332 patients in the Humira® group and 341 patients in the ENTYVIO group.
‖The commonly used immunomodulators in the order of greatest to least were azathioprine, mercaptopurine, and methotrexate.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Infusion-Related and Hypersensitivity Reactions:** 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 click for additional Important Safety Information.

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VARSITY TRIAL

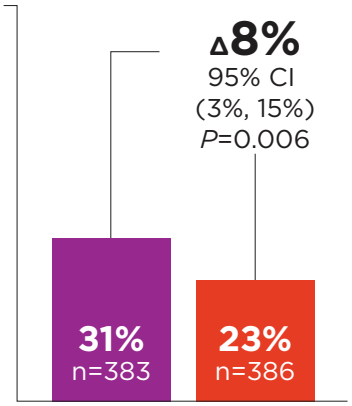
ENTYVIO DEMONSTRATED SUPERIORITY TO HUMIRA® IN CLINICAL REMISSION AT WEEK 52[1]

Overall population

PRIMARY END POINT WEEK 52

ENTYVIO IV Humira® (adalimumab)

Clinical remission[1]*



> "For me, the most compelling aspect of the VARSITY trial is that it **demonstrated the superiority of ENTYVIO to Humira® in achieving clinical remission at 52 weeks."**

*Clinical remission was defined as a complete Mayo Score of ≤2 points and no subscore >1 point.
CI=confidence interval.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Infections:** 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.

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SAFETY PROFILE[1,3,4]

Study was not designed to assess safety differences

No new safety signals were observed for ENTYVIO[1,3,4]

ADVERSE REACTIONS

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

- The most frequent AEs* for Humira® 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 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. 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 1 dose of the study drug.

†No cases of progressive multifocal leukoencephalopathy.

‡Not related to ENTYVIO.

§Updated to include final 68-week safety follow-up.

AE=adverse event; TEAE=treatment-emergent adverse event.

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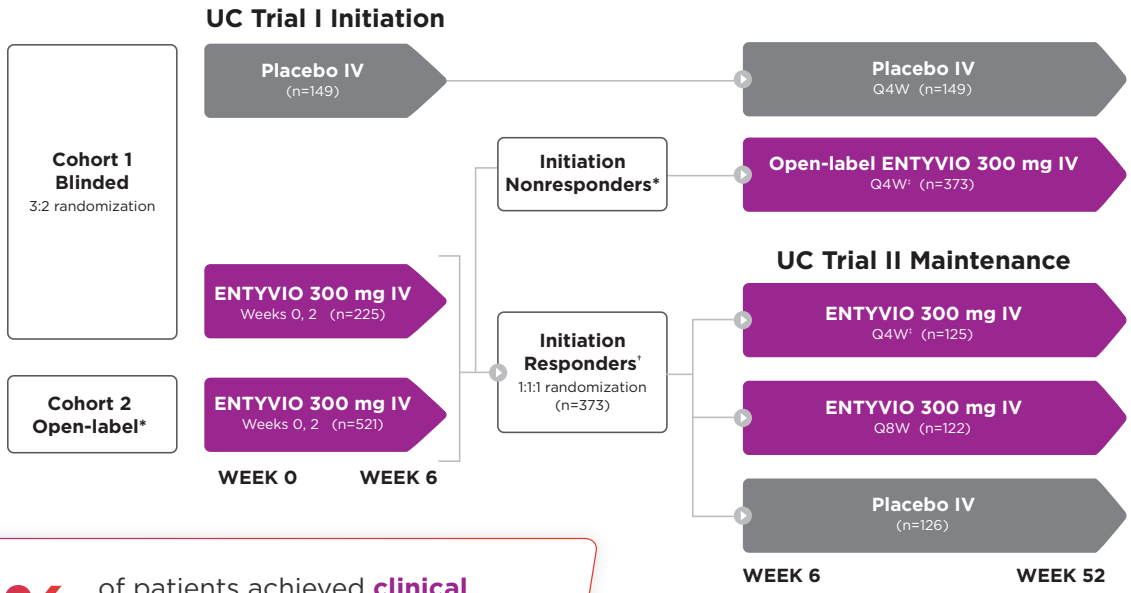
GEMINI I TRIAL

STUDY DESIGN[5-7]

- Ulcerative Colitis Trials I and II were randomized, double-blind, placebo-controlled studies that enrolled adult patients who had moderately to severely active ulcerative colitis and had failed ≥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 induction



53% of patients achieved **clinical response to ENTYVIO at Week 6**

Primary End Points[6]
Clinical response at Week 6
Clinical remission at Week 52

*Not included in efficacy analysis.

†Clinical response=reduction in complete Mayo Score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. Nonresponders (n=373) received open-label ENTYVIO Q4W for up to 52 weeks (not included in Ulcerative Colitis Trial II efficacy analysis).

‡The ENTYVIO Q4W dosing regimen did not demonstrate additional clinical benefit over the Q8W dosing regimen and is not the recommended dosing regimen

IV=intravenous; Q4W=every 4 weeks; Q8W=every 8 weeks; TNFα=tumor necrosis factor alpha.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Progressive Multifocal Leukoencephalopathy (PML):** 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 typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported. Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms that may 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 neurologist; if confirmed, discontinue ENTYVIO dosing permanently.

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GEMINI I TRIAL

PRIMARY END POINTS

Overall population compared with placebo

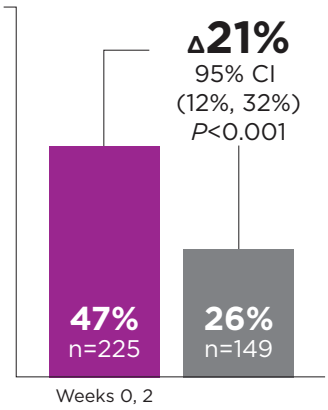
ENTYVIO-treated patients achieved

RAPID RESPONSE AND LONG-TERM REMISSION

ENTYVIO IV Placebo

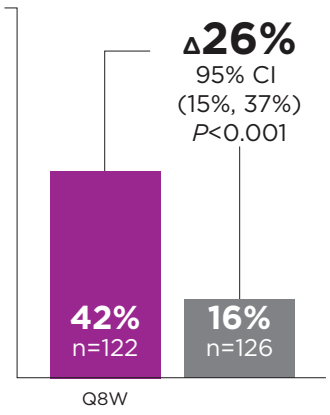
WEEK 6

Clinical response[5]*



WEEK 52

Clinical remission[5]†



*Clinical response=reduction in complete Mayo Score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

†Clinical remission=complete Mayo Score of ≤2 points and no individual subscore >1 point.

CI=confidence interval; Q8W=every 8 weeks.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Liver Injury:** 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.

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GEMINI TRIALS I AND II

SAFETY PROFILE

ENTYVIO vs placebo:

A PROVEN SAFETY PROFILE

BASED ON 4 CLINICAL TRIALS[5]

ADVERSE REACTIONS OBSERVED IN THE GEMINI TRIALS[5]

Adverse reactions in ≥3% of ENTYVIO-treated patients and ≥1% higher than in placebo (UC Trials I and II* and Crohn's disease Trials I and III*)

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

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (nonresponders at Week 6 of UC Trial I and CD Trial I) are included.
†Patients who received ENTYVIO for up to 52 weeks.
‡Patients who received placebo for up to 52 weeks.

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Adverse events observed in UC Trials I and II and Crohn's disease Trials I and III[5]

INFECTIONS

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 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

IMMUNOGENICITY

The rate of detectable anti-vedolizumab antibodies at any time during the 52 weeks of continuous treatment with ENTYVIO was 6% (86 of 1427 patients).

- 20 of 86 patients were persistently positive (at 2 or more consecutive study visits) for anti-vedolizumab antibody, and 56 of 86 patients developed neutralizing antibodies to vedolizumab
- Among these 20 patients, 14 had undetectable or reduced vedolizumab serum concentrations. Five of the 20 patients with persistently positive anti-vedolizumab antibody achieved clinical remission at Week 52 in the controlled trials
- Overall, there was no apparent correlation of anti-vedolizumab antibody development to adverse reactions following intravenous administration of ENTYVIO

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

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 (eg, human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm^3 and prior and concomitant immunosuppression)

LIVER INJURY

ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

3 patients reported serious adverse reactions of hepatitis with ENTYVIO; 1 additional case of serious hepatitis was seen in the open-label trial.

- These adverse reactions occurred following 2 to 5 ENTYVIO doses; however, it is unclear if the reactions indicated drug-induced or autoimmune etiology
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO
- All patients recovered following discontinuation of therapy with or without treatment with corticosteroids

MALIGNANCIES

Malignancies (excluding dysplasia and basal cell carcinoma) were reported in 0.4% (6 of 1434) of patients treated with ENTYVIO and in 0.3% (1 of 297) of patients treated with placebo.

- The number of malignancies in clinical trials was small; however, long-term exposure was limited

ADVERSE REACTIONS

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

INFUSION-RELATED REACTIONS (IRRs) AND HYPERSENSITIVITY REACTIONS

4% of patients treated with ENTYVIO (N=1434) experienced an IRR vs 3% of patients on placebo (N=297).

- 1 case of anaphylaxis (1 of 1434 patients treated with ENTYVIO) 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 IV hydrocortisone
- **Most frequently observed IRRs** in patients treated with ENTYVIO were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria, and vomiting. These reactions generally occurred within the first 2 hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment

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> **ENTYVIO is a good option as a first-line biologic in adults with moderate to severe UC** with its established safety profile and proven efficacy over the long term."*
>
> **– DR. STEPHEN HANAUER**

*In clinical trials, patients had previously demonstrated an inadequate response to or intolerance of conventional treatments (corticosteroids or immunomodulators) and/or anti-tumor necrosis factor therapies.[5]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

WARNINGS AND PRECAUTIONS

- **Infusion-Related and Hypersensitivity Reactions:** 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.
- **Infections:** 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):** 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 typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported. Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms that may 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 neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- **Liver Injury:** 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.
- **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 and may receive live vaccines if the benefits outweigh the risks.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥3% and ≥1% higher than placebo) were: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, pain in extremities, and injection site reactions with subcutaneous administration.

DRUG INTERACTIONS

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab products and with TNF blockers. Upon initiation or discontinuation of ENTYVIO in patients treated with CYP450 substrates, monitor drug concentrations or other therapeutic parameters, and adjust the dosage of the CYP substrate as needed.

INDICATIONS

Adult Ulcerative Colitis (UC):
ENTYVIO is indicated in adults for the treatment of moderately to severely active UC.

Adult Crohn's Disease (CD):
ENTYVIO is indicated in adults for the treatment of moderately to severely active CD.

DOSAGE FORMS & STRENGTHS:

- ENTYVIO Intravenous (IV) Infusion: 300 mg vedolizumab
- ENTYVIO Subcutaneous (SC) Injection: 108 mg vedolizumab

Please click for Full Prescribing Information.

References: 1. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. *N Engl J Med*. 2019;381(13):1215-1226. **2.** Macaluso FS, Maida M, Grova M, et al. *Therap Adv Gastroenterol*. 2021;14:1-11. **3.** Data on file. Takeda Pharmaceuticals. **4.** Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. *N Engl J Med*. 2019;381(13):1215-1226. (supplemental appendix). **5.** ENTYVIO (vedolizumab) prescribing information. Takeda Pharmaceuticals. **6.** Feagan BG, Rutgeerts P, Sands BE, et al; for the GEMINI 1 Study Group. *N Engl J Med*. 2013;369(8):699-710. **7.** Feagan BG, Rutgeerts P, Sands BE, et al; for the GEMINI 1 Study Group. *N Engl J Med*. 2013;369(8):699-710 (supplemental appendix).

If you are a Colorado prescriber, please see the Colorado WAC **disclosure form**. If you are a Connecticut prescriber, please see the Connecticut WAC **disclosure form**.

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