# THE GI PERSPECTIVE

ISSUE 3

**Entyvio:**
A first-line biologic for the treatment of adults with moderately to severely active ulcerative colitis or Crohn's disease when other therapies have not worked well enough or cannot be tolerated[1]

FEATURING
## BINCY ABRAHAM, MD, MS

*"Entyvio has demonstrated efficacy and safety that support my decision to use it first line when treating moderately to severely active UC and CD. In my opinion, the gut selectivity of Entyvio is another attribute that is notable for an advanced therapy."*


Dr. Bincy Abraham is a paid consultant of Takeda Pharmaceuticals, Inc.

## 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.

**Please see additional Important Safety Information on page 8 and full Prescribing Information, including Medication Guide.**

Entyvio® vedolizumab

> *"Today we have many advanced therapies to treat UC and CD, but that makes it harder to decide which to use first."*

SCAN OR CLICK TO ACCESS FULL INTERVIEW

## DR. BINCY ABRAHAM

- Associate Professor of Clinical Medicine in the Academic Division of Gastroenterology and Hepatology at Houston Methodist, Weill Cornell, Houston, TX
- Chair of the Southern Texas Chapter of the Crohn's & Colitis Foundation Medical Advisory Committee
- Internationally recognized clinical trialist and expert in the treatment of inflammatory bowel disease

CD=Crohn's disease; UC=ulcerative colitis.

# Entyvio (vedolizumab):

## A first-line advanced* therapy for the treatment of adults with moderately to severely active ulcerative colitis and Crohn's disease when other therapies have not worked well enough or cannot be tolerated[1]

Examining challenges when starting advanced therapy in UC and CD and how Entyvio may help with **Dr. Bincy Abraham**

**Q:** ***What are your considerations when deciding on a first-line advanced therapy for moderately to severely active UC or CD?***

With so many options, it's complex to decide where to start. Key factors I consider include disease severity and location, presence of complications, and inflammatory or other comorbidities. Patient preferences like administration, lifestyle, and safety are important because I want a medication that the patients will stick with.

**Q:** ***What information do you rely on when selecting a first-line advanced therapy in UC or CD?***

Clinical trial data, head-to-head study data, and long-term data from pivotal studies, registries, and real-world evidence. These data help me inform patients on risks versus benefits of treatment. There are treatment guidelines for UC and CD from our national societies; however, we personalize our therapy to our patients.

**Q:** ***How do you sequence Entyvio in your treatment paradigm for UC and CD?***

Entyvio is an appropriate first-line advanced therapy option for my patients with moderately to severely active UC or CD because of its safety and efficacy data, especially in either TNF-naïve or failure patients.

**Q:** ***What attributes of Entyvio do you find most attractive for the treatment of moderately to severely active UC or CD?***

The most informative data for Entyvio were remission rates at 1 year and long-term safety in both UC and CD. The responses observed in the VARSITY trial in moderate-to-severe UC were also noteworthy. Lastly, Entyvio is a gut-selective therapy, which my patients like to learn about when I offer it as a treatment option.

*Advanced: immunosuppressants or biologics used after failure of conventional therapies.
CD=Crohn's disease; UC=ulcerative colitis.

## 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 8 and full Prescribing Information, including Medication Guide.**

Entyvio® vedolizumab

# ENTYVIO COMBINES GUT SELECTIVITY, LONG-TERM REMISSION, AND SAFETY DATA FOR THE LONG TERM

## GUT SELECTIVITY

Entyvio helps address inflammation where it occurs—in the gut.[2-7]

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

## LONG-TERM REMISSION

UC and CD patients achieved remission at Week 52 versus placebo in study populations that included bio-naïve and anti-TNFα-experienced patients.[1,8]

**Individual results may vary**

## SAFETY DATA FOR THE LONG TERM

Clinical trials evaluated safety in more than 3300 patients (UC and CD). A separate open-label study of up to 7 years demonstrated consistent results across safety parameters.[1,9-11*]

***Q:** How would you describe the MOA of Entyvio to a colleague?*

In inflammatory bowel disease, specific memory T-lymphocytes use α4β7 integrins to squeeze through endothelial cells and get into the gut. Entyvio blocks these integrins, preventing these lymphocytes from getting into the gut and causing inflammation.[1]

SCAN OR CLICK TO ACCESS MOA VIDEO

*In a single-arm, open-label extension study of 2243 patients who received Entyvio with a median cumulative exposure of 42.4 months in patients with UC and 31.5 months in patients with CD.[9]
CD=Crohn's disease; GI=gastrointestinal; MAdCAM-1=mucosal addressin cell adhesion molecule-1; MOA=mechanism of action; TNFα=tumor necrosis factor alpha; UC=ulcerative colitis.

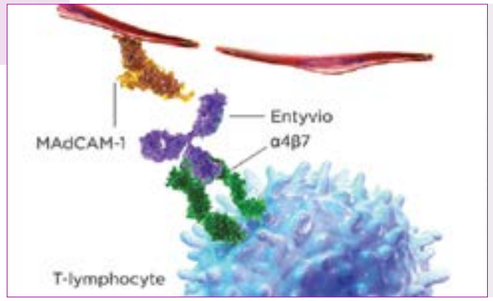
## IMPORTANT SAFETY INFORMATION

- 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 postmarketing 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.

**Please see additional Important Safety Information on page 8 and full Prescribing Information, including Medication Guide.**

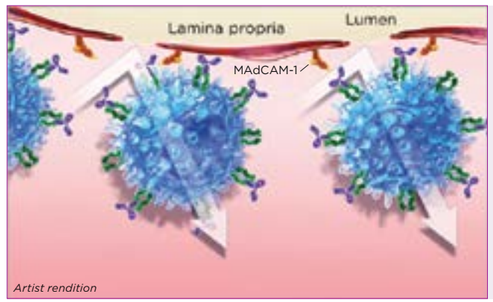
GUT SELECTIVITY

# ENTYVIO: THE FIRST AND ONLY THERAPY WITH A GUT-SELECTIVE MECHANISM OF ACTION




## Entyvio blocks lymphocyte interaction[1]

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.[1-7]



*Artist rendition*

## Inflammation is reduced[1]

T-lymphocyte migration into the gut is inhibited and inflammation is reduced.

***Q:** What do patients typically want to know about how Entyvio works?*

Patients love to hear that Entyvio acts specifically in the GI tract to help control damaging inflammation. I find describing how the therapy works helps engage patients in their treatment.

GI=gastrointestinal; MAdCAM-1=mucosal addressin cell adhesion molecule-1.

## 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 8 and full Prescribing Information, including Medication Guide.**

Entyvio® vedolizumab

LONG-TERM REMISSION

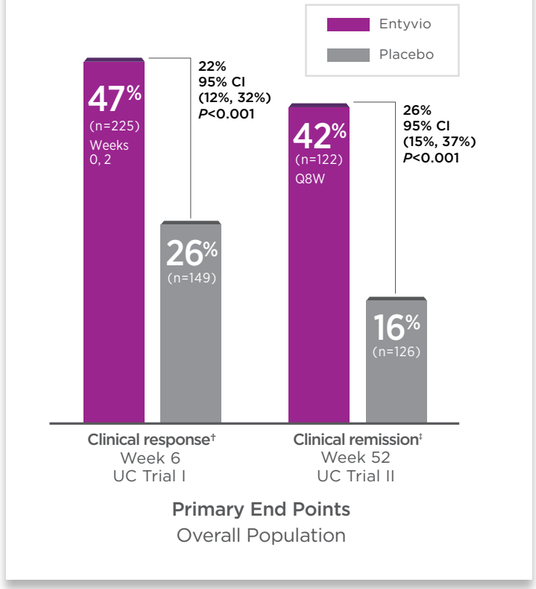
# ENTYVIO FOR UC: RAPID RESPONSE AND LONG-TERM REMISSION

## GEMINI 1 (UC Trials I and II) Study Design[1]

Two randomized, double-blind, placebo-controlled studies 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. In UC Trial I, patients were randomized (3:2) to receive Entyvio 300 mg or placebo by intravenous infusion at Weeks 0 and 2. In UC Trial II, patients receiving Entyvio who demonstrated clinical response at Week 6 (from UC Trial I or an open-label cohort) were randomized (1:1:1) to receive either Entyvio 300 mg every 8 weeks, Entyvio 300 mg every 4 weeks,* or placebo every 4 weeks.

SCAN OR CLICK FOR MORE GEMINI 1 DATA

## GEMINI 1 Primary End Points[1]




***Q: What do you find most pertinent about the GEMINI 1 results?***

**The GEMINI 1 results demonstrated that Entyvio worked quickly. At Week 6, a significant number of patients achieved clinical response. Long-term remission and short- and long-term safety data were consistent with my experience in clinical practice.**

*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.
†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.
‡Clinical remission: complete Mayo score of ≤2 points and no individual subscore >1 point.
CI=confidence interval; 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.
- 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.

**Please see additional Important Safety Information on page 8 and full Prescribing Information, including Medication Guide.**

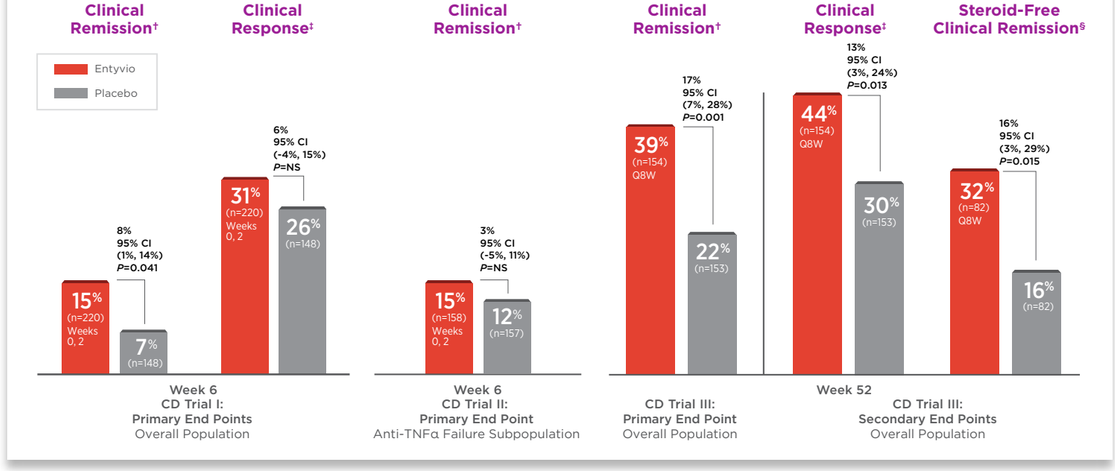
# ENTYVIO FOR CD: DEMONSTRATED LONG-TERM REMISSION

## GEMINI 2 (CD Trials I and III) and 3 (CD Trial II) Study Design[1,8,12]

Three randomized, double-blind, placebo-controlled studies enrolled adult patients with moderately to severely active CD who had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or ≥1 anti-TNFα therapy. Concomitant aminosalicylates, corticosteroids, and immunomodulators were permitted in all 3 trials. In CD Trial I, patients were randomized (3:2) to receive Entyvio 300 mg or placebo by intravenous infusion at Weeks 0 and 2. In CD Trial II, patients were randomized (1:1) to receive either Entyvio 300 mg or placebo at Weeks 0, 2, and 6. In CD Trial III, patients receiving Entyvio who demonstrated clinical response (≥70-point decrease in CDAI score from baseline) at Week 6 (from CD Trial I or an open-label cohort) were randomized (1:1:1) to receive either Entyvio 300 mg every 8 weeks, Entyvio 300 mg every 4 weeks,* or placebo every 4 weeks.

SCAN OR CLICK FOR MORE GEMINI 2 DATA

## GEMINI 2 and 3 Study End Points[1,8,12]




***"The significant clinical remission results at Week 52 in patients with moderate-to-severe CD were notable from GEMINI 2, as well as the safety profile observed in this study."***

*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.
†Clinical remission=CDAI score ≤150.
‡Clinical response=≥100-point decrease in CDAI from baseline.
§Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response (defined as ≥70 decrease in CDAI from baseline) at Week 6 (n=82 for placebo and n=82 for Entyvio every 8 weeks). Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.
CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CI=confidence interval; NS=not significant; Q4W=every 4 weeks; Q8W=every 8 weeks; TNFα=tumor necrosis factor alpha.

## IMPORTANT SAFETY INFORMATION

- 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.

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Entyvio® vedolizumab

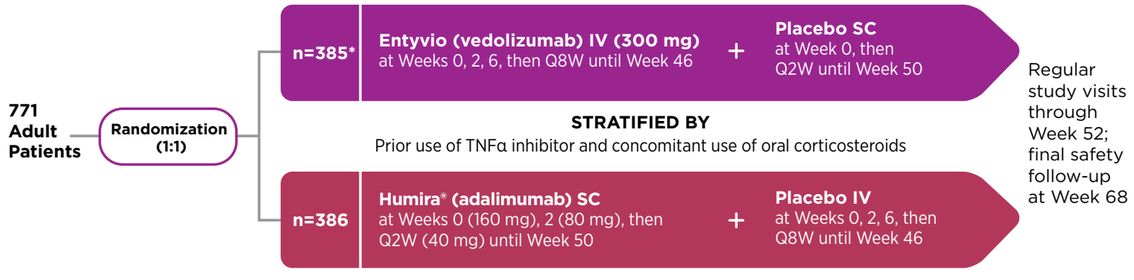
# ONLY ENTYVIO OFFERS RESULTS FROM THE FIRST HEAD-TO-HEAD STUDY OF BIOLOGICS IN MODERATE-TO-SEVERE ULCERATIVE COLITIS

***Q: What is the value of head-to-head data when making treatment decisions in UC?***

There is huge value in head-to-head data. These studies are the gold standard for comparative data.

SCAN OR CLICK FOR MORE VARSITY DATA

## VARSITY Study Design[13]




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

- 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. 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[13]
- Dosing was consistent with the US product label for both Entyvio and Humira®; no dose escalation was permitted for either treatment group[13]
- After induction, patients remained in their respective treatment groups throughout the maintenance phase (treat-through design)[13]
- Enrollment, capped at 25% (~21% was reached), included patients who discontinued treatment with an anti-TNFα (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[13,14]
- 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[13,14]

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

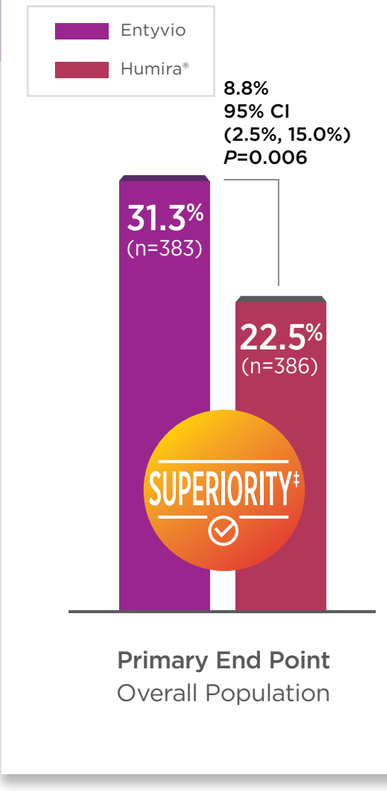
## IMPORTANT SAFETY INFORMATION

- 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 8 and full Prescribing Information, including Medication Guide.**

# ENTYVIO DEMONSTRATED SUPERIORITY TO HUMIRA® (ADALIMUMAB) IN THE PRIMARY END POINT OF CLINICAL REMISSION AT WEEK 52 IN THE OVERALL POPULATION

**CLINICAL REMISSION RATES AT WEEK 52[13*†]**




> ***"VARSITY provided comparative information about Entyvio and Humira® on clinical remission, showing that Entyvio was superior."***

## Adverse Events in the Safety Population

**VARSITY was not designed to assess safety differences.[15]**

- Adverse events§ occurred in 62.7% of the patients (240 of 383) in the vedolizumab group and in 69.2% (267 of 386) in the adalimumab group. Serious adverse events‖ occurred in 11.0% of the patients (42 of 383) in the Entyvio group and in 13.7% (53 of 386) in the adalimumab group[13]
- The most frequent AEs§ reported 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%[14]

**For full VARSITY safety data, visit EntyvioHCP.com by using the QR code to the left.**

*Clinical remission was defined as a complete Mayo score of ≤2 points and no subscore >1 point.[13]
†Full analysis set includes all randomized patients who received at least 1 dose of study drug.[13]
‡Superiority was demonstrated in the overall population.[13]
§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.[13]
‖No cases of progressive multifocal leukoencephalopathy.[13]
AE=adverse event; CI=confidence interval; TEAE=treatment-emergent adverse event.

## 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.

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Entyvio® vedolizumab

SAFETY DATA FOR THE LONG TERM

# ENTYVIO: UP TO 7 YEARS OF CONSISTENT SAFETY DATA IN UC AND CD

## GEMINI LTS Study Design[9]

**Study Design/Methodology**

GEMINI LTS was a phase 3, single-arm, open-label, multinational study evaluating the long-term safety profile of Entyvio in patients with moderately to severely active UC or CD.

- Patients were enrolled from the phase 3 studies GEMINI 1, GEMINI 2, GEMINI 3, and a long-term phase 2 study, and included a cohort of Entyvio-naïve patients with UC and CD. Data were collected from May 2009 to October 2017
- The study evaluated 2243 UC and CD patients who received any dose of Entyvio in the study
- The safety population included all patients who received any dose of Entyvio

SCAN OR CLICK FOR MORE GEMINI SAFETY DATA

**Baseline characteristics**

**EXPOSURE TO STUDY DRUG IN THE PHASE 3 STUDY POPULATION (N=2243)[9,11]**

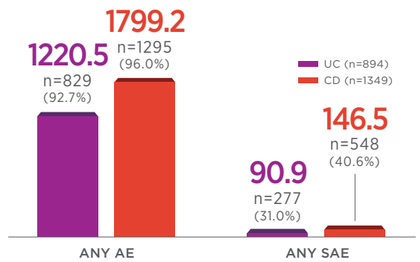
- **≥1 years** n=1629 (73%)
- **≥2 years** n=1350 (60%)
- **≥3 years** n=1164 (52%)
- **≥4 years** n=1006 (45%)
- **≥5 years** n=780 (35%)
- **≥6 years** n=556 (25%)
- **≥7 years** n=263 (12%)
- **≥8 years** n=79 (4%)
- **≥9 years** (n=5, all UC)

**MEDIAN ENTYVIO EXPOSURE IN UC: 42.4 MONTHS, RANGE 0.03-112.2 MONTHS**
**MEDIAN ENTYVIO EXPOSURE IN CD: 31.5 MONTHS, RANGE 0.03-100.3 MONTHS**

*"UC and CD are chronic diseases that patients will have for the rest of their lives. It's critical that we choose a therapy that will not only work for them over the long term but also has a demonstrated safety profile."*

**EXPOSURE-ADJUSTED INCIDENCE RATES OF ANY AE OR SAE[9]**

Number of patients with event/1000 PYs of exposure*




*Time-adjusted incidence rate per 1000 PYs=(number of patients experiencing an AE of interest/total person time in years) x 1000.

AE=adverse event; CD=Crohn's disease; LTS=long-term safety; PY=patient-year; SAE=serious adverse event; 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.

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# ENTYVIO: UP TO 7 YEARS OF CONSISTENT SAFETY DATA IN UC AND CD

## No new safety signals up to 7 years in UC and CD patients

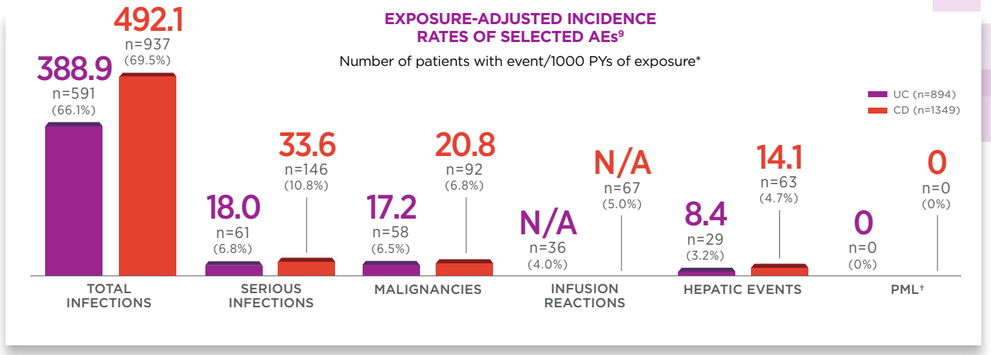
**NO NEW SIGNALS OF[10]:**

Infections
Malignancies
Infusion-related reactions
Hepatic injury

- The most frequent AEs were disease exacerbations (35.9% UC, 35.3% CD), nasopharyngitis (28.2% UC, 25.4% CD), and arthralgia (17.3% UC, 24.4% CD)[9]
- 39.7% of AEs in UC and 46.2% of AEs in CD were considered by the treating physician to be related to exposure to Entyvio[9]

**EXPOSURE-ADJUSTED INCIDENCE RATES OF SELECTED AEs[9]**

Number of patients with event/1000 PYs of exposure*




- GEMINI LTS identified no cases of PML with 7999 PYs of Entyvio exposure†

*Time-adjusted incidence rate per 1000 PYs=(number of patients experiencing an AE of interest/total person time in years) x 1000.
†Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms.[1]
AE=adverse event; CD=Crohn's disease; LTS=long-term safety; N/A=not available; PML=progressive multifocal leukoencephalopathy; PY=patient-year; UC=ulcerative colitis.

*"The Entyvio safety profile is consistent for up to 7 years. It hasn't changed over time. The side effects of GEMINI LTS align with those of previous studies."*

## 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.
- 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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Entyvio® vedolizumab

SAFETY DATA FOR THE LONG TERM

# ENTYVIO: LONG-TERM SAFETY DATA IN UC AND CD

*"Although there is no drug without any potential for side effects, Entyvio has shown consistent tolerability in my practice, which reassures my patients."*

## Select Adverse Events Observed in UC Trials I and II and CD Trials I and III[1]

| Category | Entyvio | Placebo |
|---|---|---|
| **Infection Rates** | 0.85 per patient-year | 0.7 per patient-year |
| **Serious Infection Rates** | 0.07 per patient-year | 0.06 per patient-year |
| **Adverse Reaction Rates** | 52% (N=1434) | 45% (N=297) |
| **Malignancy Rates** | 0.4% (N=1434) | 0.3% (N=297) |
| **Immunogenicity Rates** | 6% (N=1427) | N/A |
| **Infusion-Related Reaction Rates** | 4% (N=1434) | 3% (N=297) |
| **Liver Injury** | 3 patients (N=1434) reported serious adverse reactions of hepatitis with Entyvio; 1 additional case of serious hepatitis was seen in the open-label trial of Entyvio. | |

Clinical trials evaluated safety in more than 3300 patients (UC and CD).[1]

CD=Crohn's disease; UC=ulcerative colitis.

## 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.

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# ADVERSE EVENTS BASED ON UC TRIALS I AND II AND CD TRIALS I AND III[1]

### 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 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 (e.g., 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 transaminases 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 CD 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** 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

CD=Crohn's disease; IV=intravenous; UC=ulcerative colitis.

## 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 8 and full Prescribing Information, including Medication Guide.**

Entyvio® vedolizumab

> ***The GEMINI trials demonstrated clinical remission through Week 52, and VARSITY provided comparative information on clinical remission, showing that Entyvio was superior to Humira® at Week 52 in the overall population. GEMINI LTS showed consistent safety for up to 7 years. All these trials further support my decision to use Entyvio for my patients.***

**Q: *How do you discuss Entyvio as a therapeutic option with your patients?***

I explain the importance of not waiting to treat their UC or CD. We discuss Entyvio's efficacy and safety data, and I emphasize the 7 years of safety data. Sharing my own clinical experience with using the medication encourages my patients.

**Q: *How did VARSITY shift your perception of Entyvio for UC?***

To me, the main perception shift triggered by VARSITY was that Entyvio worked better than Humira® at the primary end point of improving clinical remission rates at Week 52.

**Q: *What has your experience been when discussing the safety profile of Entyvio with your patients?***

Patients are concerned about the safety of any medical therapies, especially advanced therapies for UC or CD. The long-term safety profile of Entyvio is reassuring.

**Q: *Why is it important to take a proactive approach when treating patients with UC and CD?***

It's important to take a proactive approach when treating patients to help address disease activity as early as possible. Also, proactively treating patients helps implement a shared decision-making approach.

CD=Crohn's disease; IBD=inflammatory bowel disease; UC=ulcerative colitis.

LTS=long-term safety.

## 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.

**Please see additional Important Safety Information on page 8 and full Prescribing Information, including Medication Guide.**

## 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 postmarketing 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 full Prescribing Information, including Medication Guide.**

Entyvio® vedolizumab


## 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 8 and full Prescribing Information, including Medication Guide.**

**References: 1.** Entyvio (vedolizumab) prescribing information. Takeda Pharmaceuticals. **2.** Briskin M, Winsor-Hines D, Shyjan A, et al. *Am J Pathol*. 1997;151(1):97-110. **3.** Fedyk ER, Wyant T, Yang L-L, et al. *Inflamm Bowel Dis*. 2012;18(11):2107-2119. **4.** Milch C, Wyant T, Xu J, et al. *J Neuroimmunol*. 2013;264(1-2):123-126. **5.** Soler D, Chapman T, Yang L-L, Wyant T, Egan R, Fedyk ER. *J Pharmacol Exp Ther*. 2009;330(3):864-875. **6.** Wyant T, Leach T, Sankoh S, et al. *Gut*. 2015;64(1):77-83. **7.** Wyant T, Fedyk E, Abhyankar B. *J Crohns Colitis*. 2016;10(12):1437-1444. **8.** Data on file. MLN0002, Final CSR C13007, October 2012. Takeda Pharmaceuticals USA, Inc. **9.** Loftus EV Jr, Feagan BG, Panaccione R, et al. *Aliment Pharmacol Ther*. 2020;52(8):1353-1365. **10.** Data on file. Internal communication, October 2020. Takeda Pharmaceuticals USA, Inc. **11.** Data on file. MLN0002, Final CSR C13008, July 2018. Takeda Pharmaceuticals USA, Inc. **12.** Sandborn WJ, Feagan BG, Rutgeerts P, et al. *N Engl J Med*. 2013;369(8):711-721. **13.** Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. *N Engl J Med*. 2019;381(12):1215-1226. **14.** Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. *N Engl J Med*. 2019;381(12):1215-1226 [supplementary appendix]. **15.** Data on file. VARSITY protocol, March 2017. Takeda Pharmaceuticals USA, Inc.

If you are a Colorado prescriber, please see the WAC disclosure form at www.Takeda.com/EntyvioCOPricing.



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