# THE GI PERSPECTIVE

ISSUE 2

**ENTYVIO:** A biologic for the treatment of adults with moderately to severely active Crohn's disease.

FEATURING

## Asher Kornbluth, MD

Dr. Asher Kornbluth is a paid consultant of Takeda Pharmaceuticals, Inc.

> **"The most compelling aspect of the GEMINI II results is the implication for long-term remission."**
>
> Remission was evaluated at Week 52.[1,2]

## 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.

**Please click for additional Important Safety Information.**

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> **ENTYVIO is a good option as a first-line biologic in Crohn's.*** It is gut selective, has a well-studied safety profile, and has been proven to be effective over the long term."

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.[1,3-8]

*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.[1]

## Dr. Asher Kornbluth

- Clinical Professor of Medicine, Icahn School of Medicine at Mount Sinai
- Gastroenterologist, New York Gastroenterology Associates
- Internationally recognized expert on IBD who has received numerous teaching awards and is extensively published on the topic of IBD management

GI=gastrointestinal; IBD=inflammatory bowel disease; MAdCAM-1=mucosal addressin cell adhesion molecule-1.



# INCLUDING A CLOSER LOOK AT THE GEMINI II TRIAL with Dr. Asher Kornbluth

### What do you find most compelling about ENTYVIO for the treatment of moderately to severely active Crohn's?

For me, the most compelling aspects of ENTYVIO are its gut-selective mechanism of action*, the long-term safety profile, and the efficacy over an extended period of time. When choosing a biologic to treat Crohn's disease, it's reassuring to have an option with up to 7 years of safety data.

*ENTYVIO specifically binds to the α4β7 integrin and blocks its interaction with MAdCAM-1, which is mainly expressed on the GI tract endothelial cells.

### ENTYVIO was approved in 2014. How has your approach to the use of ENTYVIO for Crohn's changed over time?

When ENTYVIO was first approved for Crohn's, I primarily used it in patients who had failed a TNFα therapy. With my experience over time, I have come to use ENTYVIO as a first-line biologic option. In particular, for the treatment of the moderately active Crohn's patient in whom other therapies have not worked well enough or cannot be tolerated.

### Approximately how many patients has your practice started on ENTYVIO?

Since the launch of ENTYVIO, my practice has started approximately 200 patients on ENTYVIO, and roughly half of those patients had moderately to severely active Crohn's disease.

### How would you describe the GEMINI II trial?

GEMINI II was one of the pivotal ENTYVIO studies in moderately to severely active Crohn's. The patient population included both anti-TNFα-naïve and anti-TNFα-experienced patients. The study was a randomized, parallel-group, double-blind, placebo-controlled trial designed to assess clinical response and clinical remission at Week 6 and clinical remission at Week 52.

TNFα=tumor necrosis factor alpha.

## 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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For adults with moderately to severely active Crohn's disease.

# PUT ENTYVIO FIRST FOR LONG-TERM RELIEF AND REMISSION*

*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.[1]

## Treat Early

**The moment your adult patients with moderate to severe Crohn's or UC are not well-controlled with conventional therapies, seek long-term relief and remission.** Patients achieved remission at Week 52 vs placebo.[1]

**Individual results may vary.**

## Treat Directly

**ENTYVIO helps address inflammation where it occurs—in the gut.[1]** ENTYVIO specifically binds to the α4β7 integrin and blocks its interaction with MAdCAM-1, which is mainly expressed on the GI tract endothelial cells.[1,3-8]

A WELL-STUDIED SAFETY PROFILE WITH UP TO

## 7 Years of Consistent Safety Results

Clinical trials evaluated safety in more than 3300 adults (UC, Crohn's, and healthy volunteers).[1] A separate open-label study of up to 7 years demonstrated **consistent results across safety parameters.[1,9,10†]**

†In a single-arm, open-label extension study, 2243 patients received ENTYVIO with a median exposure of 1072 days (range 1 to 3412 days).[9,10]

**"ENTYVIO is a gut-selective therapy for Crohn's that has been on the market since 2014. It has an established safety profile and has proven to be effective over the long term."**

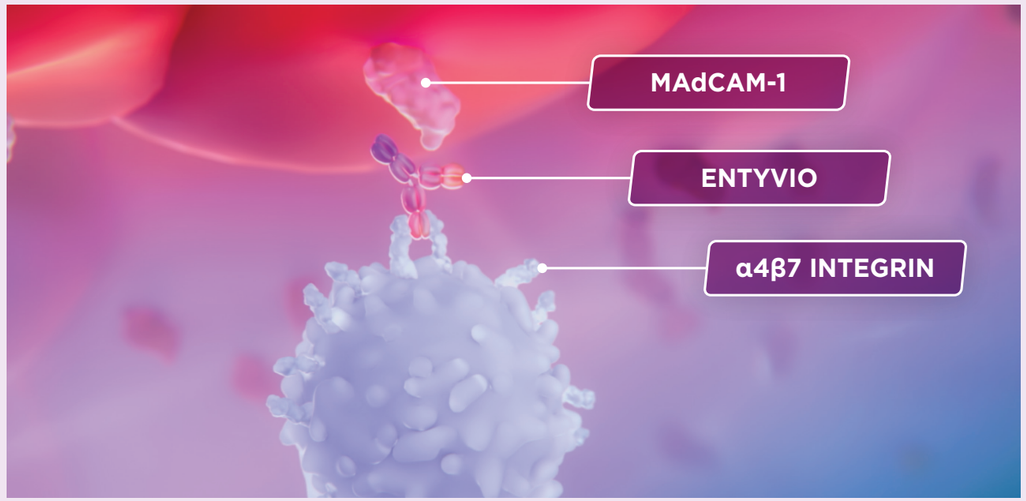
GI=gastrointestinal; MAdCAM-1=mucosal addressin cell adhesion molecule-1; UC=ulcerative colitis.



# ENTYVIO: A THERAPY WITH A GUT-SELECTIVE MECHANISM OF ACTION

### How do you describe the mechanism of action of ENTYVIO to patients?

I like to keep it simple. I let them know that ENTYVIO is gut selective and blocks certain inflammatory cells within the GI tract. The drug is reserved for where it is needed, the GI tract.




### ENTYVIO helps address inflammation where it occurs—in the gut[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[1,3-8]
- As a result, certain lymphocytes are blocked from entering the GI tract, and gut inflammation is selectively reduced[1,6,8]

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

## 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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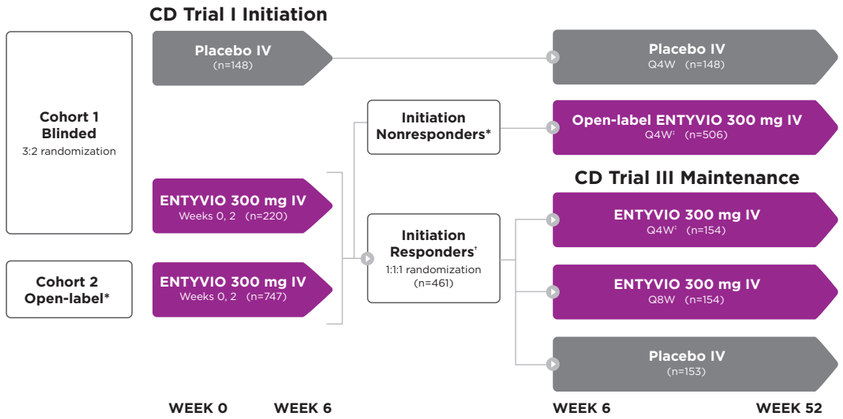
# DESIGNED TO ASSESS REMISSION AT WEEK 6 AND WEEK 52 IN CROHN'S

## STUDY DESIGN[1,2,10]




*Not included in efficacy analysis.
†Initiation response=≥70-point decrease in CDAI from baseline. Nonresponders (n=506) received open-label ENTYVIO Q4W for up to 52 weeks (not included in CD Trial III 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.

- CD Trials I and III were randomized, double-blind, placebo-controlled studies that enrolled adult patients with moderately to severely active Crohn's who had failed at least one conventional therapy, including corticosteroids or immunomodulators and/or ≥1 TNFα therapy[1]
- Concomitant aminosalicylates and corticosteroids were permitted through Week 52. Concomitant immunomodulators were permitted outside the US but were discontinued after Week 6 in the US[1]

### GEMINI III Study Design

In GEMINI III, (N=416) patients were randomized (1:1) to receive either ENTYVIO 300 mg (n=157) or placebo (n=158) at Weeks 0, 2, and 6. A majority (76%) of enrolled patients had an inadequate response, loss of response, or intolerance to ≥1 TNF blocker; this was the primary analysis population. The primary end point for GEMINI III was the proportion of patients achieving clinical remission (CDAI score ≤150) at Week 6. Secondary end points, including assessment at Week 10, were not tested because treatment with ENTYVIO did not result in statistically significant improvement over placebo at Week 6[1]

## 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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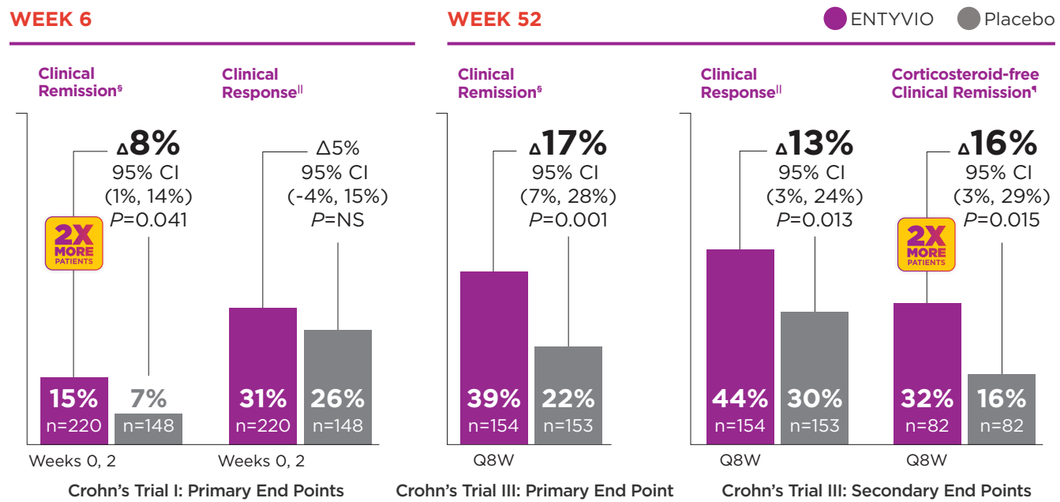
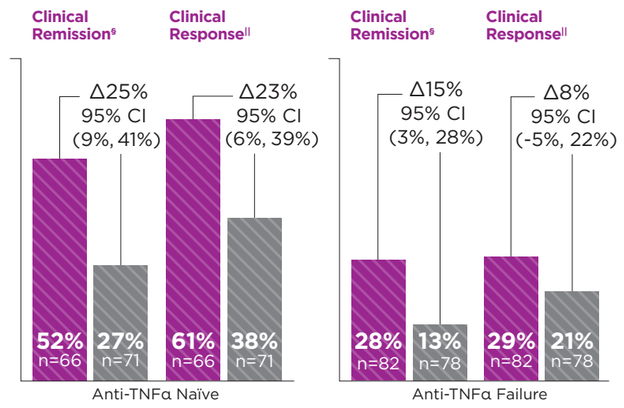
GEMINI II TRIAL

# PRIMARY, SECONDARY, AND SELECT EXPLORATORY END POINTS[1,2,10]




**"The remission data are compelling because the results demonstrated the likelihood for a patient to remain in remission at one year."**

- In a separate study (GEMINI III), 15% (n=158) of patients taking ENTYVIO who had a sub-optimal response to ≥1 anti-TNFα therapy achieved clinical remission§ at Week 6 versus 12% (n=157) with placebo (*P*=NS) (primary end point, GEMINI III)[1]

§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.

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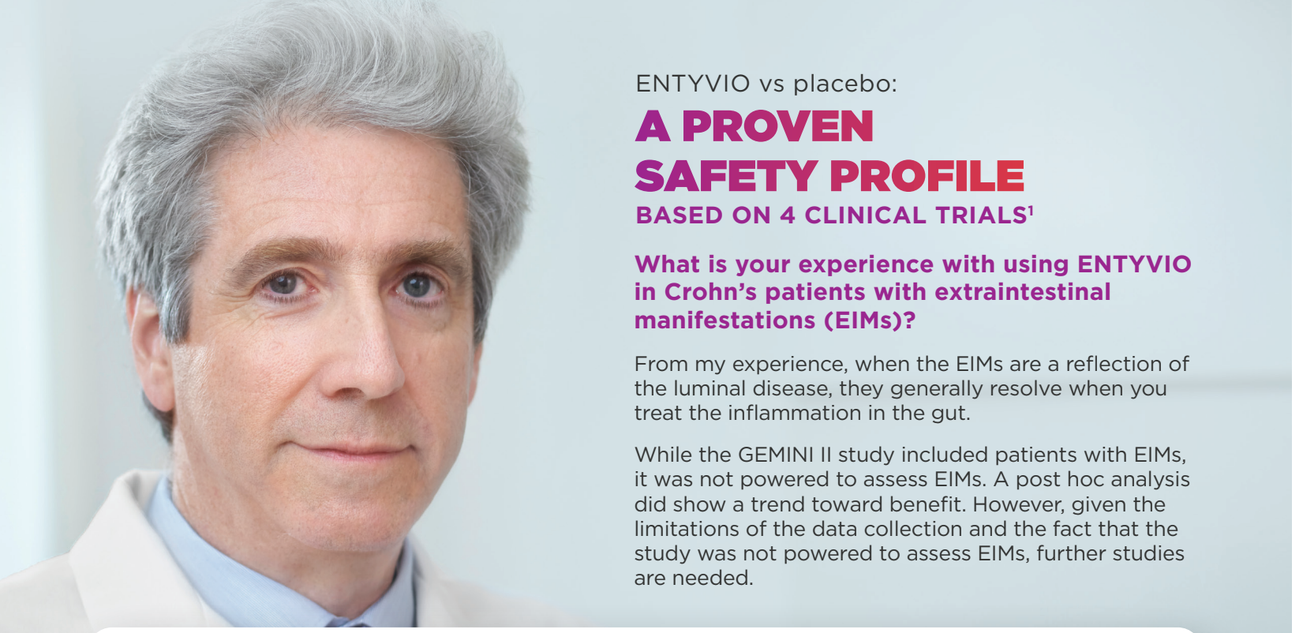

ENTYVIO vs placebo:

# A PROVEN SAFETY PROFILE

## BASED ON 4 CLINICAL TRIALS[1]

### What is your experience with using ENTYVIO in Crohn's patients with extraintestinal manifestations (EIMs)?

From my experience, when the EIMs are a reflection of the luminal disease, they generally resolve when you treat the inflammation in the gut.

While the GEMINI II study included patients with EIMs, it was not powered to assess EIMs. A post hoc analysis did show a trend toward benefit. However, given the limitations of the data collection and the fact that the study was not powered to assess EIMs, further studies are needed.

### ADVERSE REACTIONS OBSERVED IN THE GEMINI TRIALS[1]

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





# Adverse events observed in 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 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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## Can you speak to your patients' experiences following initiation of therapy?

My experiences with patient-reported outcomes are similar to those that were seen in the exploratory analysis of Crohn's Trials I, II, and III. In those trials, both loose stool frequency and abdominal pain were assessed as early as Week 2.

## Can you describe the type of Crohn's patient who best responds to ENTYVIO?

Based on post hoc analyses, the ideal patient for ENTYVIO is the bio-naïve patient in whom conventional therapies have not worked well enough. You don't want to wait until the patient develops severe disease, as duration of disease is an important predictor of success.

We know from the GEMINI studies that a moderate patient will tend to have a more robust response to ENTYVIO. Ultimately, further investigation is needed to identify the patient type who best responds to ENTYVIO.

## What is your experience with using ENTYVIO in Crohn's patients with small bowel disease?

In the GEMINI II trial, approximately 7 out of 10 patients had a component of small bowel Crohn's disease. While those patients weren't studied as a separate cohort, they were included in both the primary and secondary end points that demonstrated clinical remission and response at Week 52. ENTYVIO may be a good choice for patients with ileocolitis, ileitis, or Crohn's colitis.



# 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

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- **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.** ENTYVIO (vedolizumab) prescribing information. Takeda Pharmaceuticals. **2.** Sandborn WJ, Feagan BG, Rutgeerts P, et al. *N Engl J Med.* 2013;369(8):711-721. **3.** Briskin M, Winsor-Hines D, Shyjan A, et al. *Am J Pathol.* 1997;151(1):97-110. **4.** Fedyk ER, Wyant T, Yang L-L, et al. *Inflamm Bowel Dis.* 2012;18(11):2107-2119. **5.** Milch C, Wyant T, Xu J, et al. *J Neuroimmunol.* 2013;264(1-2):123-126. **6.** Soler D, Chapman T, Yang L-L, Wyant T, Egan R, Fedyk ER. *J Pharmacol Exp Ther.* 2009;330(3):864-875. **7.** Wyant T, Leach T, Sankoh S, et al. *Gut.* 2015;64(1):77-83. **8.** Wyant T, Fedyk E, Abhyankar B. *J Crohns Colitis.* 2016;10(12):1437-1444. **9.** Loftus EV Jr, Feagan BG, Panaccione R, et al. *Aliment Pharmacol Ther.* 2020;52(8):1353-1365. **10.** Data on file. Takeda Pharmaceuticals. **11.** Feagan BG, Sandborn WJ, Colombel J-F, et al. *J Crohns Colitis.* 2019;13(1):50-57.

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“**ENTYVIO is a good first-line option for the adult bio-naïve patient with moderately active Crohn’s.** The gut-selective mechanism of action, coupled with a demonstrated safety profile and long-term efficacy, make ENTYVIO an appealing choice for my patients.”

**– DR. ASHER KORNBLUTH**

Remission was evaluated at Week 52.[1]
Individual results may vary.

## ENTYVIO MECHANISM OF ACTION[1,3-8]

- ENTYVIO works through a gut-selective MOA by specifically binding to the α4β7 integrin and blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells

## 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.

**Please click for additional Important Safety Information.**

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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