Vedolizumab (ENTYVIO) for Intravenous Injection

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Vedolizumab is a monoclonal antibody that specifically binds to the α4ß7 integrin and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal (GI) parenchymal tissue, which in theory, decreases inflammation in the GI tract. It was developed in an attempt to confer gut selectivity and avoid negative adverse reactions seen with closely related biologics, notably natalizumab, which has been associated with life-threatening progressive multifocal leukoencephalopathy (PML).
- Vedolizumab was FDA-approved for induction and maintenance therapy in adults with moderately to severely active ulcerative colitis and for achieving (but not maintaining) clinical response and remission in adults with moderately to severely active Crohn's disease in patients who have failed at least one conventional therapy (i.e., glucocorticoids, immunomodulators, or tumor necrosis factor (TNF) antagonists).
- Moderate-quality evidence suggests that vedolizumab is efficacious in the induction and maintenance of remission of ulcerative colitis (NNT of 9 for clinical remission at week 6; NNT of 7 for maintaining durable clinical remission).
- In Crohn's disease, vedolizumab showed inconsistent efficacy in inducing remission (NNT of 13 in one trial; no benefit in another trial). It also achieved clinical remission temporarily but did not show durable benefit (or gain FDA approval) for maintenance of remission. It lacked benefit in inducing clinical response or remission in TNF antagonist failures by week 6.
- No head-to-head trials of vedolizumab versus active comparators have been performed. Indirect comparisons suggest that vedolizumab is similar to TNF-antagonists in inducing remission in ulcerative colitis.
- In clinical trials, hypersensitivity reactions to vedolizumab have occurred, including a single case of anaphylaxis. Patients receiving vedolizumab may also be at an increased risk of infection. There have been reports of elevated transaminases and bilirubin in those receiving vedolizumab. Progressive multifocal leukoencephalopathy (PML) has not been reported in trials of up to 52 weeks' duration, but it cannot be ruled out as an adverse reaction to vedolizumab at this time. The most common adverse effects reported were nasopharyngitis, headache, arthralgia, and nausea. Longer-term safety trials are needed to further assess the risks of PML and other potential harms. Based on evidence to date, one important potential safety advantage of vedolizumab over TNF-antagonists is a lack of association with disseminated opportunistic infections.
- Conclusion: Vedolizumab is a novel agent that specifically targets the α4β7 integrin of the gastrointestinal tract. The numbers needed to treat in ulcerative colitis and Crohn's disease indicated small effects with vedolizumab therapy. However, these numbers must be interpreted in the context of prior treatment attempts. In somewhat treatment-refractory ulcerative colitis and Crohn's disease populations with high morbidity, vedolizumab appears to have a role in improving clinically meaningful outcomes, although there is much less trial data and clinical experience with vedolizumab than TNF-antagonists. As with other biologics for ulcerative colitis, the evidence supports reserving the use of vedolizumab for those patients who have previously failed at least one conventional treatment (i.e., glucocorticoid, immunomodulator, or TNF antagonist). For Crohn's disease, the evidence supports a limited role and is conflicting regarding use in TNF antagonist failures. Concomitant immunosuppressive therapy may prevent formation of human antihuman

antibodies to vedolizumab; however, the relative efficacy of combination therapy has not been evaluated. A mostly third-line role for vedolizumab in moderately to severely active inflammatory bowel diseases can be justified based on several factors, including relatively limited efficacy and safety data, lack of long-term safety information, requirement for administration in a health care setting, and potential for serious adverse events.

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Introduction

Vedolizumab is the second humanized monoclonal antibody targeted against α4 integrin that the FDA has approved for use in Crohn's disease. It is the first to also receive an indication for use in ulcerative colitis. Unlike natalizumab, which also targets α4 integrin, vedolizumab is selective for the α4β7 integrin, which is thought to confer selectively for receptors in the gastrointestinal tract. One aim of designing a gut-selective agent was to potentially reduce the risk of progressive multifocal leukoencephalopathy (PML), a rare but life-threatening side effect of natalizumab that initially caused it to be withdrawn from the market.

The majority of FDA panelists voted to approve vedolizumab for induction and maintenance in both ulcerative colitis and Crohn's disease, and it was approved as such on May 20, 2014. The majority voted to approve vedolizumab for use in patients who have failed one or more glucocorticoid, immunosuppressant, or TNFα-antagonist, though a minority dissented that the indication should not include patients who have failed glucocorticoid only. The rationale for the dissent was that patients who had failed glucocorticoids alone were not included in vedolizumab trials conducted in the United States. However, these patients were included in studies conducted in other countries.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating vedolizumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Mechanism of Action

Vedolizumab is a humanized IgG_1 monoclonal antibody produced in Chinese hamster ovary cells that specifically binds to α4ß7 integrin and blocks the interaction of α4ß7 integrin with mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal (GI) parenchymal tissue. Vedolizumab does not bind to or inhibit function of the α4ß1 and αEß7 integrins and does not antagonize the interaction of α4 integrins with vascular cell adhesion molecule-1 (VCAM-1).

The α4ß7 integrin is expressed on the surface of a discrete subset of memory T-lymphocytes that preferentially migrate into the GI tract. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T-lymphocytes to gut lymph tissue. The interaction of the α4ß7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of ulcerative colitis (UC) and Crohn's disease (CD).

Pharmacokinetics

Similar pharmacokinetics were observed in UC and CD patients who received 300 mg infusions at weeks 0 and 2, followed by 300 mg infusions every 8 weeks starting from week 6 (Table 1).

Table 1: Mean SD Vedolizumab Concentrations by Condition

Patient Population	Weeks 0-6: Trough Serum Concentration at Week 6	Weeks 6 to 52: Trough Serum Concentration at Week 46
Ulcerative Colitis	26.3 ± 12.9 (N=210)	11.2 ± 7.2 (N=77)
Crohn's Disease	27.4 ± 19.2 (N=198)	13.0 ± 9.1 (N=72)

Data from UC Trials I and II and CD Trials I and III. Patients with anti-vedolizumab antibodies excluded.

Patients who developed anti-vedolizumab antibodies were observed to have either undetectable or negligible levels of vedolizumab at weeks 6 and 52 (n=8).

Vedolizumab is cleared by both linear and nonlinear pathways. The nonlinear clearance decreases with increasing concentration. The serum half-life is approximately 25 days at the 300-mg dose. Volume of distribution was approximately 5 L.

In a study of 14 healthy subjects, vedolizumab was not detected in the cerebrospinal fluid five weeks after a single 450 mg infusion of vedolizumab.

FDA Approved Indication(s)

Adult Ulcerative Colitis

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

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

Adult Crohn's Disease

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

- achieving clinical response
- achieving clinical remission
- achieving corticosteroid-free remission

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

There were no studies supporting off-label uses for vedolizumab.

Alternative Agents

Ulcerative Colitis:

Glucocorticoids	
Budesonide	Nonformulary
Methylprednisolone	Formulary
Prednisolone	Nonformulary
Prednisone	Formulary
Immunomodulators	
Azathioprine	Formulary
Cyclosporine	Formulary
Mercaptopurine	Formulary
Biologics	
Adalimumab (Humira)	Nonformulary
Golimumab (Simponi)	Nonformulary
Infliximab (Remicade)	Nonformulary

Crohn's Disease:

Glucocorticoids	
Budesonide	Nonformulary
Prednisone	Formulary
Immunomodulators	
Azathioprine	Formulary
Mercaptopurine	Formulary
Methotrexate	Formulary
Biologics	
Adalimumab (Humira)	Nonformulary
Certolizumab (Cimzia)	Nonformulary
Infliximab (Remicade)	Nonformulary
Natalizumab (Tysabri)	Nonformulary

Dosage and Administration

Dosage

For adult ulcerative colitis or Crohn's disease: 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14.

No recommendations are available for dosing in special populations (renal, hepatic, elderly).

Administration

Ensure patient is up to date with all immunizations prior to initiating therapy.

Intravenous infusion over 30 minutes. Do not administer as an intravenous push or bolus. Vedolizumab lyophilized powder must be reconstituted with Sterile Water for injection and diluted in 250 mL of sterile 0.9% Sodium Chloride injection prior to administration [see Dosage and Administration (2.4)]. After the infusion is complete, flush with 30 mL of sterile 0.9% Sodium Chloride injection.

Vedolizumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.

Table 2 Comparison of Administration Between Vedolizumab and Alternative Biologics

Agent	Route	Frequency
Adalimumab	Subcutaneous	UC and CD: weeks 0 and 2, followed by every other week starting week 4
Certolizumab	Subcutaneous	CD only: weeks 0, 2, and 4, followed by every 4 weeks
Golimumab	Subcutaneous	UC only: weeks 0 and 2, followed by every 4 weeks
Infliximab	2-hour IV infusion	UC and CD: weeks 0, 2, and 6 followed by every 8 weeks
Natalizumab	1-hour IV infusion	CD only: every 4 weeks
Vedolizumab	30-minute IV infusion	UC and CD: weeks 0, 2, and 6 followed by every 8 weeks

Efficacy

Efficacy Measures

Ulcerative Colitis[6]

The primary efficacy measure evaluated in Ulcerative Colitis is the Mayo Score. Four variables make up the Mayo Score, including:

- Stool frequency, scaled from 0 (normal frequency) to 3 (5 or more stools more than normal)
- Rectal bleeding (most severe bleeding of day), on a scale of 0 (none) to 3 (blood alone passed)
- Endoscopic findings, ranged from 0-3 based on severity
- Physician's global assessment (normal – severe)

The stool frequency component of the Mayo Score is a subjective measurement based on the patient's perception of normal frequency. As such, it is susceptible to inter-patient variation in reporting.

Of note, the Mayo Score is just one of many instruments available for assessing disease severity in ulcerative colitis, and none of the instruments have been definitively validated. However, Mayo Score is noted to be one of the most widely used efficacy measures in ulcerative colitis studies. The efficacy measures used by the GEMINI 1 study group (see below) are consistent with those used to evaluate similar alternative agents and have been recognized as appropriate measures by the FDA.

Crohn's Disease

The primary efficacy measure studied in the Crohn's Disease phase 3 trial was the Crohn's Disease Activity Index (CDAI).[7] The CDAI evaluates eight weighted variables which are totaled to produce the CDAI score.

The eight CDAI variables are as follows:

- Number of liquid/soft stools daily for the last 7 days
- Abdominal pain on a scale of 0 (none) to 3 (severe)
- General well-being, on a scale of 0 (well) to 4 (terrible)
- Extra-intestinal symptoms (arthritis/arthralgia, iritis/uveitis, skin/mouth lesions, perianal disease, other fistula, or fever)
- Anti-diarrheal use
- Abdominal mass (0 = none, 2 = questionable, 5= definite)
- Hematocrit (subtracted from 47% for males or from 42% for females)
- Weight (percentage deviation from standard weight)

As with the Mayo Score for ulcerative colitis, the CDAI score is partially subjective, particularly in the fairly non-specific measure of general well-being.

A CDAI score of less than 150 is generally defined as disease remission. CDAI scores ranging from 150 to 220 indicate mild-moderate disease, 220-450 indicates moderate-severe disease, and values >450 are associated with severe, fulminant disease.

Summary of efficacy findings

Ulcerative Colitis

The GEMINI 1 trial evaluated efficacy of vedolizumab versus placebo in patients with moderate to severe ulcerative colitis.[1,3] The study included an induction phase (referred to as UC I) and a maintenance phase (UC II). Patients were eligible for inclusion if they met criteria for moderate-severe ulcerative colitis and had documented unsuccessful treatment (i.e., inadequate response, loss of response or intolerance) with glucocorticoids, purine antimetabolites (azathioprine, 6-mercaptopurine), or one or more TNF antagonists.

In the induction phase (UC I), the primary outcome was clinical response, which was defined as Mayo score reduction of at least 3 points and 30% from baseline, with a 1-point reduction or score ≤1 on the rectal bleeding subscale. Secondary outcomes included clinical remission (Mayo score ≤2 and no subscores >1), and mucosal healing on endoscopic exam (Mayo endoscopic subscore 0-1). Primary and secondary outcomes for the induction phase were evaluated after 6 weeks of therapy.

The primary outcome in the maintenance phase (UC II) was clinical remission at week 52. There were several secondary outcomes, which were evaluated in the following ranked order: durable clinical response (response at both week 6 and week 52); durable clinical remission (remission at both week 6 and week 52), mucosal healing at week 52, and glucocorticoid-free remission at week 52 (only assessed in patients on glucocorticoids at baseline).

The trials reported absolute risk reduction for vedolizumab compared to placebo as follows:

- UC I Outcomes (Induction phase of GEMINI 1)
    - Clinical response at week 6: 21.7% (NNT = 5)
    - Clinical remission at week 6: 11.5% (NNT = 9)
    - Mucosal healing at week 6: 16.1% (NNT = 7)
- UC II Outcomes (Maintenance phase of GEMINI 1)
    - Clinical remission at week 52: 26.1% (NNT = 4) for every 8 weeks; 29.1% (NNT = 4) for every 4 weeks
    - Durable clinical response at week 52: 32.8% (NNT = 4) for every 8 weeks; 28.5% (NNT = 4) for every 4 weeks
    - Mucosal healing at week 52: 32.0% (NNT = 4) for every 8 weeks; 36.3% (NNT = 3) for every 4 weeks
    - Durable clinical remission: 11.8% (NNT = 9) for every 8 weeks; 15.3% (NNT = 7) for every 4 weeks
    - Corticosteroid-free remission at week 52: 26.1% (NNT = 4) for every 8 weeks; 29.1% (NNT = 4) for every 4 weeks

Summary of findings from GEMINI 1:

- In the induction phase, vedolizumab demonstrated statistically significant benefit over placebo in all endpoints, including clinical response, clinical remission, and mucosal healing, at week 6.
- In the maintenance phase, vedolizumab was statistically superior to placebo in all primary and secondary endpoints at week 52. Outcomes were similar in the every 4-week and every 8-week vedolizumab treatment arms.

Crohn's Disease

Two phase 3 trials, GEMINI 2 and GEMINI 3, were conducted to evaluate efficacy of vedolizumab in moderately to severely active Crohn's disease.[4,5] GEMINI 2 included induction and maintenance phases (termed CD I and CD III, respectively).[4] Eligibility criteria were similar to those used for GEMINI 1, except for the additions of (1) inadequate response or intolerance to methotrexate; and (2) non-U.S. patients could enter the trial if they were glucocorticoid-dependent.

Gemini 2

In the induction phase of GEMINI 2 (CD I) the two primary endpoints were clinical remission (CDAI score ≤150) and CDAI-100 response (decrease by at least 100 points in CDAI score), both assessed at week 6. The secondary endpoint, mean change in C-reactive protein level, was also evaluated at week 6.

The maintenance phase of GEMINI 2 (CD III) used a primary endpoint of clinical remission at week 52. Secondary endpoints included CDAI-100 response at week 52, glucocorticoid-free remission (remission at week 52 without glucocorticoids), and durable clinical remission (remission at ≥80% of study visits).

Of note, the definition of "durable clinical remission" differed between the GEMINI 1 and GEMINI 2 maintenance trials. In ulcerative colitis, durable remission was only assessed at two time points (week 6 and week 52). By contrast, patients in the maintenance phase of GEMINI 2 were evaluated every 4 weeks and had to be in remission for ≥80% of clinic visits in order for their remission to be considered durable. Durable clinical remission was also evaluated at week 52 in the GEMINI 2 trial. Although durable clinical remission is an attractive outcome measure to characterize continued maintenance of remission, other biologics studied for use in Crohn's disease have not been held to the same standard. Therefore, the inability of vedolizumab to achieve "durable" clinical remission in GEMINI 2 must be interpreted with caution.

The trials reported absolute risk reduction for vedolizumab compared to placebo as follows:

- CD I Outcomes (Induction phase of GEMINI 2)
  - Clinical remission at week 6: 7.8% (NNT = 13)
  - CDAI-100 response: Not statistically significant
  - Change in CRP: Not statistically significant
- CD II Outcomes (Induction phase of GEMINI 3)
  - Clinical remission at week 6: Not statistically significant
- CD III Outcomes (Maintenance phase of GEMINI 2)
  - Clinical remission at week 52: 17.4% (NNT = 6) for every 8 weeks; 14.7% (NNT = 7) for every 4 weeks
  - CDAI-100 response at week 52: 13.4% (NNT = 8) for every 8 weeks; 15.3% (NNT = 7) for every 4 weeks
  - Corticosteroid-free remission at week 52: 15.9% (NNT = 7) for every 8 weeks; 12.9% (NNT = 8) for every 4 weeks
  - Durable clinical remission: Not statistically significant

Summary of findings from GEMINI 2:

- In the induction phase, a statistically significant benefit of vedolizumab over placebo was demonstrated in the primary endpoint of clinical remission at week 6, but not in the co-primary endpoint of CDAI-100 response or the secondary endpoint of mean change in C-reactive protein (CRP).
- In the maintenance phase, no difference was seen in the rate of durable clinical remission between vedolizumab and placebo. Statistical significance was achieved for clinical remission at week 52. The every 4-week and every 8-week treatment arms had similar outcomes.

GEMINI 3

GEMINI 3 had an induction phase only (CD II) and specifically targeted patients who failed prior TNF-α antagonist therapy (i.e., an inadequate response to, loss of response to, or intolerance of ≥1 TNF antagonists). Eligibility criteria were similar to those used in GEMINI 1 and 2. However, in contrast to GEMINI 2, which capped TNF-α antagonist failures at 50% of the participants, 75% of enrollees in GEMINI 3 had failed prior TNF-α antagonist therapy. This suggests that the GEMINI 3 study population was more treatment-refractory than those patients studied in GEMINI 2.

Vedolizumab was not statistically superior to placebo for inducing clinical response at week 6 in the TNF-antagonist failure population. However, secondary outcomes suggest that effects of vedolizumab on clinical remission may not become evident between weeks 6 and 10 in this population, which may be more treatment-resistant. An increase of remission rates in the TNF-antagonist failure population was observed between weeks 6 and 10, while remission rates in the placebo group remained similar.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 17).

Safety

Safety data were available from 3,326 patients and healthy volunteers who received vedolizumab. Of these, 1,396 were exposed to study drug for greater than one year and 835 were exposed for greater than two years.

The prescribing information reported common "Adverse Reactions" (suggesting the manufacturer deemed there was a relationship to the study drug). Where applicable, the term "adverse event" was used (indicating an event that occurred without assessment of potential causality).

Deaths and Other Serious Adverse Reactions

Thirteen deaths occurred across controlled and uncontrolled studies of vedolizumab in UC and CD studies. The FDA summary reviewer noted the risk for death is similar in patients exposed to vedolizumab and those not exposed, though this must be viewed with caution given the low event rate.[1] None of the deaths were assessed to be related to vedolizumab by the FDA reviewer. Three deaths were assessed as related by the investigator. Two were exacerbations of Crohn's Disease and were more likely related to inefficacy rather than a medication effect. A third death deemed related by the investigator was a case of hepatocellular carcinoma three years post-vedolizumab initiation. The FDA reviewer believed this was not plausibly related to vedolizumab.

Overall (two UC and two CD trials), 7% of vedolizumab patients and 4% of placebo patients experienced serious adverse reactions. Rates of specific serious adverse events were not provided in manufacturer documentation.

Common Adverse Reactions

Across UC and CD trials, 52% of vedolizumab patients and 45% of placebo patients experienced adverse reactions. The most common adverse reactions are shown in Table 3.

Table 3 Most Common Adverse Reactions (Reported in ≥ 3% of Vedolizumab-treated Patients and ≥ 1% Higher than in Placebo)

Adverse Reaction[3,4]	Vedolizumab (N=1,434)	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	3%	3%
Rash	3%	2%
Pruritis	3%	1%
Sinusitis	3%	1%
Oropharyngeal Pain	3%	1%
Pain in Extremities	3%	1%

Safety data were similar to those shown in Table 3 for 279 patients in the two UC trials and CD trials I and III who received vedolizumab at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for 416 patients in CD Trial II who received treatment for 10 weeks.

Infections

- The overall rate of infection was 0.85 per patient-year in patients treated with vedolizumab and 0.7 per patient-year in patients treated with placebo.[3,4]
- The rate of serious infection was 0.07 per patient-year in patients treated with vedolizumab and 0.06 per patient-year in patients treated with placebo.[3,4]
- Sepsis, including bacterial sepsis and septic shock, was reported in 4 (0.3%) of 1,434 patients treated with vedolizumab and in 2 (0.7%) of 297 patients treated with placebo. Two CD patients treated with vedolizumab died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with UC or CD receiving vedolizumab was 2 per 1,000 patient-years.
- Other serious infections have also been reported, including anal abscess, tuberculosis, salmonella sepsis, listeria meningitis, giardiasis and cytomegaloviral colitis.
- In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with vedolizumab. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the U.S., and none of the patients had extra-pulmonary manifestations.

Liver Injury

- There were reports of elevations of transaminase and/or bilirubin in patients receiving vedolizumab.
- In UC Trials I and II and CD Trials I and III, 3 patients reported serious adverse events of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g. malaise, nausea, vomiting, abdominal pain, anorexia). These serious adverse events (SAEs) occurred following 2 to 5 vedolizumab doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment.
- In controlled trials, the incidence of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations $\geq$ 3 x upper limit of normal (ULN) was < 2% in patients treated with vedolizumab and in patients treated with placebo.
- In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

- Malignancies (excluding dysplasia and basal cell carcinoma) were reported in 6 (0.4%) of 1,434 patients treated with vedolizumab, including colon cancer (n = 2), transitional cell carcinoma (n = 1), breast cancer (n = 1), carcinoid tumor of the appendix (n = 1) and squamous cell carcinoma (n = 1). Malignancy was reported in 1 (0.3%) of 297 patients treated with placebo (squamous cell carcinoma).[3,4]
- Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer, and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Live and Oral Vaccines

- There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab. In a placebo-controlled study of healthy volunteers, 61 subjects were given a single vedolizumab 750-mg dose (2.5 times the recommended dose), and 62 patients received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with vedolizumab did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to vedolizumab did

have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

Immunogenicity

- As with all therapeutic proteins, there is potential for immunogenicity. In UC Trials I and II and CD Trials I and III, in patients who received vedolizumab, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose).
- During treatment, 56 of 1 434 (4%) of patients treated with vedolizumab had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab.
- Among eight of these nine subjects with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations.
- None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.
- The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, presence of vedolizumab, and underlying disease. For these reasons, comparison of the incidence of antibodies to vedolizumab with the incidence of antibodies to other products may be misleading.

Contraindications

Vedolizumab is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate).

Warnings and Precautions

Infusion-Related Reactions (IRR) and Hypersensitivity

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions included a case of anaphylaxis in 1 (0.07%) of 1434 patients. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to vedolizumab may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post infusion. If anaphylaxis or other serious allergic reactions occur, discontinue administration of vedolizumab immediately and initiate appropriate treatment (eg, epinephrine and antihistamines).

Infections

Patients treated with vedolizumab are at increased risk for developing infections. The most commonly reported infections in clinical trials occurring at a rate greater on vedolizumab than placebo involved the upper respiratory tract and nasal mucosa (e.g. nasopharyngitis, upper respiratory tract infection).

Serious infections have also been reported in patients treated with vedolizumab, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

Vedolizumab is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with vedolizumab.

Exercise caution when considering the use of vedolizumab in patients with a history of recurring severe infections. Consider screening for tuberculosis according to the local practice.

Progressive Multifocal Leukoencephalopathy (PML)

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

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

Monitor patients on vedolizumab for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with vedolizumab and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

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

Live and Oral Vaccines

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

Special Populations

No recommendations are available for dosing in special populations (renal, hepatic, elderly).

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

Postmarketing Safety Experience

In its summary review, the FDA advisory committee that approved vedolizumab recommended a postmarket observational study to characterize potential risk for PML and evaluate serious risks of infections and malignancies.

A postmarketing safety study (GEMINI LTS) is ongoing, with expected completion August 2016.[8]

Sentinel Events

No data at this time

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

- LA/SA for generic name *vedolizumab*: vandetanib, vemurafenib
- LA/SA for trade name ENTYVIO: Enjuvia, Emtriva, Evizo

Drug Interactions

Drug-Drug Interactions

Natalizumab: Because of the potential for increased risk of PML and other infections, avoid the concomitant use of vedolizumab with natalizumab.

TNF-α blockers: Because of the potential for increased risk of infections, avoid the concomitant use of vedolizumab with TNF-α blockers.

Live vaccines: May be administered concurrently with vedolizumab only if the benefits outweigh the risks.

Drug-Lab Interactions

None reported.

Data Compilation Tables

All data compilation tables are adapted from the FDA summary review.[1]

Table 4 Effect Sizes for Induction Therapy in Ulcerative Colitis

Endpoint*		PBO N = 149	VDZ N = 225	P value	ARR	NNT	95% CL
1°	Clinical response at week 6	25.5%	47.1%	<0.0001	21.7%	5	11.6%, 31.7%
1st 2°	Clinical remission at week 6	5.4%	16.9%	0.0009	11.5%	9	4.7%, 18.3%
2nd 2°	Mucosal healing at week 6	24.8%	40.9%	0.0012	16.1%	7	6.4%, 25.9%

*1° = Primary end point; 1st 2° = First ranked secondary endpoint; 2nd 2° = Second ranked secondary endpoint

Source: Feagan et al. (2013)[3]

Table 5 Effect Sizes for Maintenance Therapy in Ulcerative Colitis

Endpoint*		PBO	VDZ Q8W	VDZ Q4W	VDZ Q8W vs. PBO			VDZ Q4W vs. PBO		
					P value	ARR (NNT)	95% CL	P value	ARR (NNT)	95% CL
1°	Clinical remission at week 52	15.9% (20 / 126)	41.8% (51 / 122)	44.8% (56 / 125)	<0.0001	26.1% (4)	14.9%, 37.2%	<0.0001	29.1% (4)	17.9%, 40.4%
1st 2°	Durable clinical response	23.8% (30 / 126)	56.6% (69 / 122)	52.0% (65 / 125)	<0.0001	32.8% (4)	20.8%, 44.7%	<0.0001	28.5% (4)	16.7%, 40.3%
2nd 2°	Mucosal healing at week 52	19.8% (25 / 126)	51.6% (63 / 122)	56.0% (70 / 125)	<0.0001	32.0% (4)	20.3%, 43.8%	<0.0001	36.3% (3)	24.4%, 48.3%
3rd 2°	Durable clinical remission	8.7% (11 / 126)	20.5% (25 / 122)	24.0% (30 / 125)	0.0079	11.8% (9)	3.1%, 20.5%	0.0009	15.3% (7)	6.2%, 24.4%
4th 2°	Corticosteroid-free remission at week 52	13.9% (10 / 72)	31.4% (22 / 70)	45.2% (33 / 73)	0.012	17.6% (6)	3.9%, 31.3%	<0.0001	31.4% (4)	16.6%, 46.2%

*1° = Primary end point; 1st 2° = First ranked secondary endpoint; 2nd 2° = Second ranked secondary endpoint

Source: Feagan et al. (2013)[3]

Table 6 Effect Sizes for Induction in Crohn's Disease

Endpoint		PBO N = 148	VDZ N = 220	P value	ARR	NNT	95% CI
1°	Clinical remission at week 6	6.8% (10/148)	14.5% (32/220)	0.041**	7.8%	13	1.2%, 14.3%
1st 2°	Change in CRP (mean, SD)	19.9 (30.0)	21.1 (26.9)	0.9288	0.2	NSD	--

*1° = Primary end point; 1st 2° = First ranked secondary endpoint;
**adjusted p-value for multiple comparisons of two primary endpoints (Clinical Remission or CDAI-100 response)
Source: Sandborn et al. (2013)[4]

Table 7 Effect Sizes for Induction Therapy in Crohn's Disease

Endpoint*		PBO N = 157	VDZ N = 158	P value	ARR	NNT	95% CI
1°	Clinical remission at week 6	12.1% (19/157)	15.2% (24/158)	0.4332	3.0%	NSD	--

*1° = Primary end point. Source: Sands et al. (2014)[5]

Table 8 Effect Sizes for Maintenance Therapy in Crohn's Disease

Endpoint		PBO	VDZ Q8W	VDZ Q4W	VDZ Q8W vs. PBO			VDZ Q4W vs. PBO		
					P-value	ARR (NNT)	95% CL	P value	ARR (NNT)	95% CL
1°	Clinical remission at week 52	21.6% (33/153)	39.0% (60/154)	36.4% (56/154)	0.0007	17.4% (6)	7.3%, 27.5%	0.0042	14.7% (7)	4.6%, 24.7%
1st 2°	CDAI-100 response at week 52	30.1% (46/153)	43.5% (67/154)	45.5% (70/154)	0.0132	13.4% (8)	2.8%, 24.0%	0.0053	15.3% (7)	4.6%, 26.0%
2nd 2°	Corticosteroid- free remission at week 52	15.9% (13/82)	31.7% (26/82)	28.8% (23/80)	0.0154	15.9% (7)	3.0%, 28.7%	0.0450	12.9% (8)	0.3%, 25.5%
3rd 2°	Durable clinical remission	14.4% (22/153)	21.4% (33/154)	16.2% (25/154)	0.1036	7.2% (NSD)	-1.5%, 16.0%	0.6413	2.0% (NSD)	-6.3%, 10.2%

*1° = Primary end point; 1st 2° = First ranked secondary endpoint; 2nd 2° = Second ranked secondary endpoint
Source: Sanborn et al. (2013)[4]

Systematic Reviews / Meta-analyses and Indirect Comparisons

A systematic review / meta-analysis of 10 placebo-controlled trials evaluating biologics in moderately to severely active ulcerative colitis showed comparable odds ratios (95% CIs included the value 1) for inducing clinical remission at 6 to 8 weeks in indirect comparisons between vedolizumab and each of the three TNF-antagonists approved for ulcerative colitis (adalimumab, golimumab, infliximab).[9] Six trials provided efficacy data for maintenance of remission; however, indirect comparisons between agents were not performed. The authors concluded that direct head-to-head comparative studies should be a high priority for further research.

A Cochrane systematic review / meta-analysis of four moderate- to high-quality, placebo-controlled, phase 2 and 3 vedolizumab RCTs (published in 20 reports) did not provide indirect comparisons with other agents.[10] One of the studies, a dose-ranging trial published as an abstract only, showed no significant beneficial effect in inducing endoscopic remission in 29 patients with moderately to severely active ulcerative colitis. In pooled adverse event

analyses, there was no statistically significant difference in the incidence of adverse events between vedolizumab and placebo groups (520/657, 79%, vs. 227/284, 80%, respectively). Significantly fewer vedolizumab patients than placebo patients withdrew because of adverse events (6% vs. 11%, respectively; RR 0.55, 95% CI 0.35 to 0.87; 2 RCTs, 941 patients). There was no treatment difference in the incidence of serious adverse events (12% in each treatment group; moderate quality evidence, 136 events).

The following table displays comparative numbers-needed-to-treat (NNTs) for various biologic agents. The numbers for the non-vedolizumab agents are from a 2011 systematic review and meta-analysis.[11] The vedolizumab NNTs are derived from the vedolizumab trials. Trials included in the meta-analysis varied greatly in terms of methodology, study duration, clinical outcomes, and population. Also of note, vedolizumab trials studied a significant number of patients who had previously failed TNF-antagonist trials. For the purposes of this table, "prevention of relapse" as defined by the meta-analysis was deemed to be equivalent to "durable clinical remission" as used in the vedolizumab trials. The meta-analysis calculated NNTs for anti-TNF agents by pooling clinical trial data of multiple agents.

Drug	NNT – UC Remission Induction	NNT – UC Relapse Prevention (26-56 weeks)	NNT- CD Remission Induction	NNT- CD Relapse Prevention (26-60 weeks)
Vedolizumab	9	9	13	NSD
Adalimumab			7	NSD
Certolizumab			NSD	
Infliximab	4		4	4
Natalizumab			11	5
Anti-TNF agents	4	NSD	8	4

NSD, No statistically significant difference

Pharmacoeconomic Analysis

No literature has been published to date on pharmacoeconomic evaluations of vedolizumab.

The manufacturer of vedolizumab conducted an economic analysis to assess the potential budget impact for third-party payers who choose to include vedolizumab on the formulary.[2] The projections were based on a five-year timeframe. Other biologic agents included in the model were as follows: for ulcerative colitis, infliximab, adalimumab, and golimumab; for Crohn's disease, infliximab, adalimumab, certolizumab, and natalizumab. The model factors in savings from clinical response and remission, as well as surgery avoidance. It accounted for costs including drug acquisition, administration costs, and other medical resource costs.

Based on this model, it was projected that including vedolizumab on a third-party formulary for ulcerative colitis and Crohn's disease would result in a per member per month (PMPM) budget impact of $0.002 in year 1, $0.008 in year 2, $0.015 in year 3, $0.019 in year 4, and $0.025 in year 5. This cost is primarily realized for Crohn's disease patients; in year 5, $0.024 of the PMPM budget impact comes from addition to the formulary for Crohn's disease, whereas only $0.001 of the impact is attributed to use in ulcerative colitis patients.

The manufacturer did note that these data projections were limited by the lack of available data for the TNF-α antagonist failure population, which, as noted above (see Efficacy) generally has a poor response to vedolizumab.

It is not clear what methods were used to calculate the budget impact model. The manufacturer states that clinical parameters, such as surgery avoidance, were considered in budget impact projections but is vague on how these were calculated. It is also not clear whether the theoretical population used to create the model is similar to the VA population in terms of relative number of potential vedolizumab users. Therefore, the model is of limited use in making decisions regarding potential financial impacts to the VA system.[2]

Conclusions

Vedolizumab is a novel agent that specifically targets the α4β7 integrin of the gastrointestinal tract. The numbers needed to treat in ulcerative colitis and Crohn's disease indicated small effects with vedolizumab therapy. However, these numbers must be interpreted in the context of prior treatment attempts. In somewhat treatment-refractory ulcerative colitis and Crohn's disease populations with high morbidity, vedolizumab appears to have a role in improving clinically meaningful outcomes, although there is much less trial data and clinical experience with vedolizumab than TNF-antagonists. As with other biologics for ulcerative colitis, the evidence supports reserving the use of vedolizumab for those patients who have previously failed at least one conventional treatment (i.e., glucocorticoid, immunomodulator, or TNF antagonist). For Crohn's disease, the evidence supports a limited role and is conflicting regarding use in TNF antagonist failures. Concomitant immunosuppressive therapy may prevent formation of human antihuman antibodies to vedolizumab; however, the relative efficacy of combination therapy has not been evaluated. A mostly third-line role for vedolizumab in moderately to severely active inflammatory bowel diseases can be justified based on several factors, including relatively limited efficacy and safety data, lack of long-term safety information, requirement for administration in a health care setting, and potential for serious adverse events.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline using the search terms "vedolizumab" and "Entyvio". Search results were limited to English-language, human studies. Citations listed in review articles, the AMCP dossier, and the FDA Summary Review were also searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included. In addition, GEMINI 3, a randomized controlled trial which has been completed but not submitted for publication, was also included for completeness. However, final analysis of vedolizumab data is limited to published findings from phase III randomized placebo-controlled studies.

The following pages include summaries of published phase III clinical trials.

Citation	**Feagan BG, Rutgeerts, P, Sands, B et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 2013;369(8):699-710.**
Study Goals	Determine whether vedolizumab induction and maintenance therapy for ulcerative colitis produces higher rates of clinical response and clinical remission compared to placebo.

Methods	**Study Design**
	Two integrated Phase 3 randomized, double-blind, placebo controlled trials in patients with active disease at 211 medical centers in 34 countries.
	N=895
	Induction Phase
	• Cohort 1 = blinded
	  ○ 3:2 ratio vedolizumab 300 mg IV days 1 and 15 vs. placebo
	  ○ Two stratification factors
	  ○ +/- concomitant glucocorticoid use
	  ○ +/- concomitant immunosuppressive agent use OR prior use or nonuse of TNF antagonists
	  ○ Previous TNF exposure limited to 50% of population sample
	• Cohort 2 = open label
	  ○ All receive active therapy (vedolizumab 300 mg IV at day 1 and 15)
	Maintenance Phase
	• Patients with clinical response at 6 weeks:
	  ○ Randomized 1:1:1 to vedolizumab every 8 weeks, vedolizumab every 4 weeks, or placebo for up to 52 weeks
	• Patients in cohort 1 who received placebo continued to receive placebo
	• Patients with no clinical response at 6 weeks:
	  ○ Vedolizumab every 4 weeks, followed for 52 weeks
	• Central randomization using computer-generated randomization schedules
	
	Primary Endpoints
	Induction:
	• Clinical response to vedolizumab at week 6, defined by all of the following having been met:
	  ○ A reduction in the Mayo Clinic score of ≥3 points,
	  ○ A decrease of ≥30% from the baseline score, and
	  ○ A decrease in ≥1 point on the rectal bleeding subscale or absolute rectal bleeding subscore of 0 or 1.
	Maintenance:
	• Clinical remission at week 52, defined by:
	  ○ Mayo Clinic score ≤2
	  ○ No individual subscore >1
	Secondary endpoints
	Induction:
	• Clinical remission at week 6, defined by:
	  ○ Mayo Clinic score ≤2
	  ○ No individual subscore >1
	• Mucosal healing defined by a endoscopic subscore of 0 or 1
	Maintenance:
	• Durable clinical response (response at both weeks 6 and 52)
	• Durable clinical remission (remission at both weeks 6 and 52)
	• Mucosal healing at week 52 defined by a endoscopic subscore of 0 or 1
	• Glucocorticoid-free remission at week 52 in patients receiving glucocorticoids at baseline.
	
	Length of Study
	Induction: 6 weeks
	Maintenance: 52 weeks
	
	Data analysis
	Cochran-Mantel-Haenszel chi-square test, with adjustment for stratification factors, for those achieving clinical response, clinical remission, and endoscopic healing.
	Hochberg procedure to control overall alpha error at 5% for testing of both dose regimens for each outcome.

	Analysis of covariance, with adjustment for stratification, for Mayo Clinic score changes, IBDQ scores, and fecal calprotectin concentration Missing data addressed by last observation carried forward and analyses were performed according to intention-to-treat.

Criteria	**Inclusion criteria**
	• 18-80 years of age
	• Must have active ulcerative colitis, defined as:
	  ○ Mayo Clinic score (range of 0-12 with higher scores indicating more active disease) of 6 to 12
	  ○ Sigmoidoscopy subscore must be at least 2
	  ○ Disease that extended 15 cm or more from the anal verge
	• Documentation of unsuccessful previous treatments (due to lack of response or adverse events), including one or more of:
	  ○ Glucocorticoids (non-U.S. patients only)
	  ○ Immunosuppressive medications (e.g. azathioprine, 6-mercaptopurine)
	  ○ TNF antagonists
	• Patients allowed to continue mesalamine and up to 30 mg of prednisone or equivalent per day.
	  ○ Rectal therapy with glucocorticoids or mesalamine was discontinued 2 weeks prior to screening.
	Exclusion Criteria
	• Received TNF antagonists within 60 days before enrollment
	• Received cyclosporine, thalidomide or investigational drugs within 30 days before enrollment
	• Treated previously with vedolizumab, natalizumab, efalizuman, or rituximab.
	• Medical conditions:
	  ○ Toxic megacolon
	  ○ Abdominal abscess
	  ○ Symptomatic colonic stricture
	  ○ Stoma
	  ○ History of colectomy
	  ○ Increased risk of complicated infections
	  ▪ Recent pyogenic infection
	  ▪ Enteric pathogens detected on stool analysis
	  ▪ Latent tuberculosis
	  ▪ Immunodeficiency
	  ▪ Hepatitis B or C, or recent live vaccination
	  ○ Clinically meaningful laboratory abnormalities
	  ○ Pregnancy or lactation
	  ○ Unstable or uncontrolled medical disorders
	  ○ Anticipated requirements for major surgery
	  ○ Colonic dysplasia or adenomas
	  ○ Malignant neoplasms

Results	**Prior Treatments in Induction Study Population:** Of the 225 vedolizumab-treated patients: 56% had used glucocorticoid; 33% immunomodulators; and 42% TNF-antagonists; an additional 36% were TNF-antagonist failures. **Prior Treatments in Maintenance Study Population:** Of 247 vedolizumab patients: 58% had used corticosteroids; 36% immunomodulators; and 41% TNF-antagonists; an additional 34% had failed TNF-antagonists. **Induction Therapy – Outcome Measures at Week 6**

Outcome	Placebo (n=149)	Vedolizumab (N=225)	% Difference (95% CI)	P value
Clinical Response	38 (25.5%)	106 (47.1%)	21.7 (11.6-31.7)	<0.001
Clinical Remission	8 (5.4%)	38 (16.9%)	11.5 (4.7-18.3)	0.001
Mucosal Healing	37 (24.8%)	92 (40.9%)	16.1 (6.4-25.9)	0.001

Cohort 2 (open-label vedolizumab, n =521)	
Clinical Response	231(44.3%)
Clinical Remission	100 (19.2%)
Mucosal Healing	37 191 (36.7%)

Maintenance Therapy – Outcome Measures at Week 52

Outcome	Placebo (N=126)	VDZEvery 8 Wks (N=122)	VDZEvery 4 Wks (N=125)	Between Group Difference			
				Every 8 Wk. vs. Placebo % points difference (95% CI)	P value	Every 4 Wk. vs. Placebo % points difference (95% CI)	P value
	Number/Total number (percent)						
Clinical Remission	20/126 (15.9%)	51/122 (41.8 %)	56/125 (44.8%)	26.1 (14.9-37.2)	<0.001	29.1 (17.9–40.4)	<0.001
Durable Clinical Response	30/126 (23.8%)	69/122 (56.6%)	65/125 (52.0%)	32.8 (20.8-44.7)	<0.001	28.5 (16.7–40.3)	<0.001
Durable Clinical Remission	11/126 (8.7%)	25/122 (20.5 %)	30/125 (24.0%)	11.8 (3.1–20.5)	0.008	15.3 (6.2–24.4)	0.001
Mucosal Healing	25/126 (19.8%)	63/122 (51.6%)	70/125 (56.0%)	32 (20.3–43.8)	<0.001	36.3 (24.4–48.3)	<0.001
Glucocorticoid-free remission	10/72 (13.9%)	22/70 (31.4%)	33/73 (45.2%)	17.6 (3.9–31.3)	0.01	31.4 (16.6–46.2)	<0.001

Safety Results

- No difference between study groups in most commonly reported adverse events
- Serious infections were not more common in vedolizumab group than with placebo
- No cases of PML
- 1 death: 14 days after administration, attributed to Acute Coronary Syndrome
- No hematological, serum chemical profiles or liver function test differences.
- Three cases of infusion reaction (2 w/ detectable anti-vedolizumab antibodies)
- No serum sickness
- No anaphylaxis

Conclusions

Vedolizumab was more effective than placebo as induction and maintenance therapy for ulcerative colitis.

Critique

Strengths

- Randomized, double-blind, placebo controlled trial
- Open-label induction cohort had similar results to blinded vedolizmab treatment group.

Limitations

- Ideal time of induction therapy not established
- No minimally effective dose established – no efficacy differences between regimens.
- Substance abuse and active psychiatric problems not defined well – may limit generalizablity

Citation	**Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *New Eng J Med.* 2013;369(8): 711-721.**
Study Goals	Determine whether vedolizumab therapy provides clinical benefit to patients with Crohn's disease.
Methods	**Study Design** Phase III MC PC RCT Induction phase (6 weeks) • Cohort 1: double-blinded, 3:2 ratio of vedolizumab 300 mg IV or placebo at weeks 0 and 2 • Cohort 2: Open label (vedolizumab 300 mg IV at weeks 0 and 2) Maintenance phase (52 weeks) • Clinical responders (≥70 point decrease in CDAI score): blinded, randomized 1:1:1 to vedolizumab q8weeks, vedolizumab q4 weeks, or placebo • Non-responders: vedolizumab q4weeks *Primary Endpoints* Induction phase • Clinical remission (CDAI ≤150) • Clinical response (≥100-point decrease in CDAI) Maintenance phase • Clinical remission *Secondary Endpoints* Induction • Mean change in CRP from baseline Maintenance • CDAI-100 response • Glucocorticoid-free remission • Durable clinical remission (remission at ≥80% of study visits) **Data Analysis** • Chi-square test for CDAI-100 and clinical remission • Hochberg method/sequential testing to maintain 5% type I error • If P value was >0.05 for one primary endpoint, the other one had to be <0.025 to be considered significant • Covariance analysis for continuous outcomes (CDAI, IBDQ, and glucocorticoid use over time) • Wilcoxon rank-sum test for data on CRP

Criteria	**Inclusion criteria**
	• 18 to 80 years of age
	• Ability to voluntarily give informed consent
	• Crohn's disease duration ≥3 months
	• CDAI score 220-450 and 1 of the following:
	  ○ C-reactive protein >2.87 mg/L;
	  ○ ≥3 nonanastomotic ulcerations; or
	  ○ fecal calprotectin >250 µg/g
	• Ileal and/or colonic disease
	• Colonoscopy within 12 mo for long-standing disease
	• Inadequate response, lost response, or intolerance to corticosteroids, immunosuppressives, and/or TNF antagonists
	• Stable dose of immunosuppressives, glucocorticoids (prednisone ≤ 30 mg/day or budesonide ≤ 9 mg/day) and antibiotics allowed
	Exclusion criteria
	• Stoma, >3 small-bowel resections, short-bowel syndrome, extensive colonic resection, intestinal stricture, abdominal abscess
	• Active or latent tuberculosis
	• Cancer
	• Previous treatment with vedolizumab, natalizumab, efalizumab, or rituximab
	• Adalimumab within 30 days before enrlment
	• Infliximab or certolizumab pegol within 60 days before enrollment

Results

Efficacy Results

Induction Trial: Key Efficacy Results

Event, n (%)	Placebo (n=148)	Vedolizumab Cohort 1 (n =220)	Vedolizumab Cohort 2 (n=747)	Vedolizumab Combined (n=967)	P value*
Clinical Remission	10 (6.8)	32 (14.5)	132 (7.7)	----	0.02
CDAI-100 Response	38 (25.7)	69 (31.4)	257 (34.4)	----	0.23

*P values compare cohort 1 with placebo

Maintenance Trial: Key Efficacy Results

Event, n (%)	Placebo (n=153)	Vedolizumab (Randomized Groups) Every 8 weeks (n =154)	P value	Every 4 weeks (n=154)	P value
Clinical remission	33 (21.6%)	60 (39.0%)	<0.001	56 (36.4%)	0.004

*P values compare respective treatment groups to placebo

Safety Results

Induction Trial: Key Safety Results

Event, n (%)	Placebo (n=148)	Vedolizumab Cohort 1 (n =220)	Vedolizumab Cohort 2 (n=747)	Vedolizumab Combined (n=967)	P value*
Patients with any adverse event	88 (59)	124 (56)	426 (57)	550 (57)	0.56
Serious adverse event	9 (6)	20 (9)	52 (7)	72 (7)	0.29
Common adverse event >5%					
Nausea	9 (6)	11 (5)	47 (6)	58 (6)	0.65
Crohn's Disease	11 (7)	15 (7)	41 (5)	56 (6)	0.82
Upper respiratory tract infection	11 (7)	15 (7)	53 (7)	68 (7)	0.90
Pyrexia	2 (1)	9 (4)	40 (5)	49 (5)	0.21
Headache	12 (8)	19 (9)	54 (7)	73 (8)	0.86
Infections					
Any	26 (18)	34 (15)	127 (17)	161 (17)	0.59
Serious**	2 (1)	1 (<1)	10 (1)	11 (1)	0.57
Infusion reaction	7 (5)	6 (3)	21 (3)	27 (3)	0.31
Malignant neoplasm	0 (0)	0 (0)	1 (<1)***	1 (<1)***	0.40

*P values compare cohort 1 with placebo
***Breast cancer

Adverse Events Affecting at Least 5% of Patients Who Received Vedolizumab

Event	Placebo (N = 301) N (%)	Vedolizumab (N = 814) N (%)
Crohn's disease exacerbation	65 (21.6)	164 (20.1)
Arthralgia	40 (13.3)	110 (13.5)
Pyrexia	40 (13.3)	103 (12.7)
Nasopharyngitis	24 (8.0)	100 (12.3)
Headache	47 (15.6)	97 (11.9)
Nausea	30 (10.0)	90 (11.1)
Abdominal pain	39 (13.0)	79 (9.7)
Upper respiratory tract infection	17 (5.6)	54 (6.6)
Fatigue	14 (4.7)	53 (6.5)
Vomiting	23 (7.6)	49 (6.0)
Any serious adverse event	46 (15.3)	199 (24.4)
Any serious infection	9 (3.0)	45 (5.5)

Conclusions

- Vedolizumab, compared to placebo, was more likely to induce clinical remission at week 6, but not CDAI-100 response
- Among patients with clinical remission at week 6, clinical remission was higher among patients receiving vedolizumab every 8 weeks or every 4 weeks versus patients receiving placebo
- Modest induction response may be attributed to treatment-refractory study population

Critique	**Strengths** • Primary endpoints were well chosen: CDAI is standard tool to define disease severity, and CDAI <150 correlates with asymptomatic remission • Achieved statistically significant and clinically relevant endpoints **Limitations** • High dropout rate due to lack of efficacy • Induction phase non-responders excluded in reporting of maintenance phase results • Excluded if any substance abuse or active psychiatric condition- limits external validity to VA population

Citation	**Sands BE, Feagan BG, Rutgeerts P. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014 Sep;147(3):618-627.**
Study Goals	Evaluate efficacy and safety of vedolizumab as induction therapy in Crohn's Disease (CD), focusing on patients with previous TNF antagonist failure (~75% of enrolled patients).
Methods	**Study Design** Phase 3, double-blind, randomized controlled trial. Multicenter, multinational trial from Nov. 2010 - Apr. 2012 Induction therapy for Crohn's Disease – safety/efficacy study 10-week treatment period 1:1 randomization to receive: • 300 mg vedolizumab at weeks 0, 2, and 6 • Placebo at weeks 0, 2, and 6 Patients were stratified by TNF-antagonist failure, concomitant oral steroid use, and concomitant immunosuppressive use. **Primary Outcome** • Percentage of Participants in Clinical Remission in the Tumor Necrosis Factor Alpha (TNF-α) Antagonist Failure Subpopulation at Week 6, defined as Crohn's Disease Activity Index (CDAI) score ≤ 150 points. **Secondary Outcomes** • Percentage of Participants in Clinical Remission at Week 6 in the Overall Population at week 6 (CDAI≤150) • Percentage of Participants in Clinical Remission at Week 10 in the TNFα Antagonist Failure Subpopulation (CDAI≤150) • Percentage of Participants in Clinical Remission at Week 10 in the Overall Population (CDAI≤150) • Percentage of Participants With Sustained Clinical Remission in the TNFα Antagonist Failure Population. Sustained clinical remission is defined as a CDAI score ≤ 150 points at both Week 6 and Week 10. • Percentage of Participants With Sustained Clinical Remission in the Overall Population. Sustained clinical remission is defined as a CDAI score ≤ 150 points at both Week 6 and Week 10. • Percentage of Participants With Enhanced Clinical Response at Week 6 in the TNFα Antagonist Failure Subpopulation. Enhanced clinical response is defined as a ≥ 100-point decrease in CDAI score from Baseline. • Number of Participants With Adverse Events (AEs) from the date of first study drug administration to Week 22, through the 14 March 2012 database lock date. **Data Analysis** • Performed for patients from intention-to-treat populations who received any amount of blinded study drug. • Missing efficacy data was considered therapy failure. • All proportion based outcomes were analyzed using the Cochran-Mantel-Haenszel chi-square test with a statistical significance level of 0.05 with stratification according to TNF-antagonist failure status, concomitant corticosteroid use and concomitant immunosuppressive use. • Hochberg method was applied to each secondary outcome pair to maintain the overall type 1 error rate at a P value of .05 or less. • Power estimates for the primary and secondary outcomes were 91% and 81%–93%, respectively, on the basis of total sample sizes of 296 for the TNF antagonist–failure population and 396 for the overall population.

Criteria	**Inclusion criteria**
	• Age 18 to 80
	• Diagnosis of moderately to severely active Crohn's disease (CDAI 220-400 within 7 days prior to enrollment), and one of the following:
	  • C-reactive protein >2.87 mg/L
	  • Colonoscopy within previous 4 months with documented ulcerations
	  • Fecal calprotectin level greater than 250 mcg/g stool

	• Crohn's Disease involvement of the ileum and/or colon • Demonstrated, over the previous 5 year period, an inadequate response to, loss of response to, or intolerance of at least one conventional therapy: corticosteroids, immunosuppressives, or TNF-α inhibitors. • May be receiving a therapeutic dose of conventional therapies for inflammatory bowel disease (IBD) as defined by the protocol **Exclusion criteria** • Previous exposure to vedolizumab, natalizumab, efalizumab, or rituximab. • Concurrent pregnancy or lactation • Unstable or uncontrolled medical condition • Major neurologic disorder • General anesthesia within 30 days • Planned major surgery during during study • Previous malignancy with the exception of certain cancers for which the recurrence risk after adequate treatment is expected to be low (e.g. nonmetastatic basal cell and squamous cell skin cancers, cervical carcinoma in situ. • Active drug or alcohol dependence • Active psychiatric disease • Evidence of abdominal abscess at the initial screening visit • Extensive colonic resection, subtotal or total colectomy • History of >3 small bowel resections or diagnosis of short bowel syndrome • Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine • Chronic hepatitis B or C infection; human immunodeficiency virus (HIV) infection • Active or latent tuberculosis

Results

Primary Outcome:

Clinical Remission in TNF- α Antagonist Failure Subpopulation at Week 6

	Vedolizumab	Placebo	Risk Difference (95% CI)	P-value
Number of Participants Analyzed	157	158	3.0% (-4.5-10.5)	0.4332
Percentage of Participants in Clinical Remission (95% CI)	12.1% (7.0-17.2)	15.2 % (9.6-20.8)		

Secondary Outcomes:

Percentage of Participants in Clinical Remission at Week 6 in the Overall Population

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	207	209	6.9% (0.1-13.8)	15	0.048
Percentage of Participants in Clinical Remission (95% CI)	12.1% (7.6-16.5)	19.1% (13.8-24.5)			

Percentage of Participants in Clinical Remission at Week 10 in the TNFα Antagonist Failure Subpopulation

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	157	158	14.4% (5.7-23.1)	7	0.001
Percentage of Participants in Clinical Remission (95% CI)	12.1% (7.0-17.2)	26.6% (19.7-33.5)			

Percentage of Participants in Clinical Remission at Week 10 in the Overall Population

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	207	209	15.5% (7.8-23.3)	7	<0.001
Percentage of Participants in Clinical Remission (95% CI)	13.0% (8.5-17.6)	28.7% (22.6-34.8)			

Percentage of Participants with Sustained Clinical Remission in the TNFα Antagonist Failure Population (Clinical Remission at Week 6 and Week 10)

	Placebo	Vedolizumab	Risk Difference (95% CI)	P-value
Number of Participants Analyzed	157	158	3.7% (-2.9-10.3)	P=.276
Percentage of Participants in Clinical Remission (95% CI)	8.3% (4.0-12.6)	12.0 (7.0-17.1)		

Percentage of Participants with Sustained Clinical Remission in the Overall Population (Clinical Remission at Week 6 and Week 10)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	207	209	7.0% (0.9-13.1)	15	0.025
Percentage of Participants w/ CDAI-100 response (95% CI)	8.2% (4.5-12.0)	15.3% (10.4-20.2)			

Percentage of Participants with Enhanced Clinical Response at Week 6 in the TNFα Antagonist Failure Population (100-point decrease in CDAI score from Baseline)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	157	158	16.9% (6.7-27.1)	6	0.001
Percentage of Participants w/ CDAI-100 response (95% CI)	22.3% (15.8-28.8)	39.2% (31.6-46.9)			

Percentage of Participants with Enhanced Clinical Response at Week 6 in the Overall Population (100-point decrease in CDAI score from Baseline)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	207	209	16.4% (7.7-25.5)	7	0.0002
Percentage of Participants w/ CDAI-100 response	22.7%	39.2%			

Percentage of Participants with Enhanced Clinical Response at Week 10 in the TNFα Antagonist Failure Population (100-point decrease in CDAI score from Baseline)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	157	158	22.0% (11.4-32.6)	5	<0.0001
Percentage of Participants w/ CDAI-100 response	24.8%	46.8%			

Percentage of Participants with Enhanced Clinical Response at Week 10 in the Overall Population (100-point decrease in CDAI score from Baseline)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	207	209	23.7% (14.5-32.9)	5	<0.0001
Percentage of Participants w/ CDAI-100 response	24.2%	47.8%			

Percentage of Participants in Clinical Remission at Week 6 in the TNF-Antagonist-Naïve Population

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	50	51	19.2% (3.3-35.0)	6	0.012
Percentage of Participants in Clinical Remission	12.0%	31.4%			

Percentage of Participants in Clinical Remission at Week 10 in the TNF-Antagonist-Naïve Population

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	50	51	19.1% (2.4-35.8)	6	0.025
Percentage of Participants in Clinical Remission	16.0%	35.3%			

Percentage of Participants with Sustained Clinical Remission in the TNF-Antagonist-Naïve Population (Clinical Remission at Week 6 and Week 10)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	50	51	17.3% (2.9-31.6)	6	0.018
Percentage of Participants in Clinical Remission	8.0%	25.5%			

Percentage of Participants with Enhanced Clinical Response at Week 6 in the TNF-Antagonist Naive Population (100-point decrease in CDAI score from Baseline)

	Placebo	Vedolizumab	Risk Difference (95% CI)	P-value
Number of Participants Analyzed	50	51	15.0% (-2.2-32.2)	0.088
Percentage of Participants w/ CDAI-100 response	24.0%	39.2%		

Percentage of Participants with Enhanced Clinical Response at Week 10 in the TNF-Antagonist Naive Population (100-point decrease in CDAI score from Baseline)

	Placebo	Vedolizumab	Risk Difference (95% CI)	NNT	P-value
Number of Participants Analyzed	50	51	28.9% (10.3-47.5)	4	0.02
Percentage of Participants w/ CDAI-100 response	22.0%	51.0%			

Adverse Events

Sixty percent of placebo-treated patients and 56% of vedolizumab-treated patients experienced one or more adverse events during the study. Drug-related serious adverse events and serious infections occurred in <1% of patients in both placebo and vedolizumab groups. Two percent in both groups discontinued the study due to serious adverse events. No deaths were reported. The most common adverse events were nausea, vomiting, headache, upper respiratory tract infection, arthralgia, nasopharyngitis and abdominal pain. No cases of PML were reported. Infusion-related adverse events aoccurred in 4 vedolizumab-treated patients and in 2 placebo-treated patients.

Conclusions

Vedolizumab was not statistically superior to placebo for inducing clinical response at week 6 in the TNF-antagonist failure population. However, secondary outcomes suggest that effects of vedolizumab on clinical remission may not become evident between weeks 6 and 10 in this population, which may be more treatment-resistant. An increase of remission rates in the TNF-antagonist failure population was observed between weeks 6 and 10, while remission rates in the placebo group remained similar.

Critique

Strengths

- Studied TNF-antagonist failure population in comparison to overall and TNF-antagonist naïve populations
- Double-blind, randomized placebo-controlled trial
- Safety profile similar to longer-term vedolizumab studies.

Limitations

- Short duration
- Only studied induction therapy – no further data on maintenance
- Active psychiatric disease exclusion criteria undefined – may limit external validity.