CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125476Orig1s000

MEDICAL REVIEW(S)

Medical Officer Clinical Review Addendum: BLA 125476
Division of Gastroenterology and Inborn Error Products

BLA Number:	**125,476**
Established name:	**Vedolizumab**
Trade Name:	**Entyvio**
Therapeutic Class:	**Integrin Receptor Antagonist**
Dosing Regimen:	**300 mg IV at 0, 2, and 6 weeks, and then every 8 weeks thereafter**
Applicant:	**Takeda**
Intended Population:	**Adult patients with moderately to severely active ulcerative colitis as defined by the Mayo Score**
Submit Date:	**June 20, 2013**
PDUFA Goal Date:	**Original - February 18, 2014** **3-month extension – May 20, 2014**
Clinical Reviewer:	**Laurie Muldowney, MD**

1. Explanation of Need for Clinical Review Amendment

This document is an addendum to a clinical review completed and finalized in DARRTS on November 20, 2013.

The original clinical review stated that the Applicant adequately demonstrated the efficacy of vedolizumab and that the benefit of vedolizumab outweighs its potential risks for adult patients with moderately to severely active ulcerative colitis. However outstanding issues related to vedolizumab for ulcerative colitis remained at that time, including:

- The key safety issue was the potential risk of progressive multifocal leukoencephalopathy (PML). There was uncertainty about the adequacy of the safety database to provide an acceptable pre-marketing assessment of this risk of PML or if continued risk evaluation and mitigation strategies (REMS) are needed in the postmarketing setting. This was to be discussed at an Advisory Committee Meeting on December 9, 2013.
- Although a relationship between concomitant immunosuppressive therapies with infections was not found, there remained the concern that the risk of infections and of PML might be higher with concomitant immunosuppressive therapies. In the vedolizumab trials, these considerations led to the requirement that concomitant immunosuppressants were not allowed beyond the induction phase in the US trials. The review team questioned whether the labeling should have similar restrictions. This was to be discussed at an Advisory Committee Meeting on December 9, 2013.
- Similarly, due to the potential risk for PML, vedolizumab use was limited to patients who failed immunomodulator or TNFα antagonist therapy in US trials, whereas outside the US prior corticosteroid failure was sufficient for inclusion. The review team questioned if vedolizumab should be indicated only for those patients who failed immunomodulator and/or TNFα antagonist therapy, or if prior corticosteroid failure should be sufficient. This was to be discussed at an Advisory Committee Meeting on December 9, 2013.

- A small number of potential cases of drug related liver injury were reported and this information became known to the review team at the time of the 120-day Safety Update. Additional information was forthcoming from the Applicant at the time of the original clinical review.

Since the original clinical review was finalized, a joint meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee was held to discuss the efficacy and safety of vedolizumab and the postmarket risk management strategy. In addition, the clinical site inspections were completed, and the Applicant provided more detailed information on 4 potential cases of drug induced liver injury, as well as updated PML and exposure data.

These updates to the original clinical review are summarized below with an updated risk/benefit assessment.

2. Recommendations/Risk Benefit Assessment

a. Recommendation on Regulatory Action

It is the recommendation of this reviewer that vedolizumab be approved for the indication of:

> inducing and maintaining clinical response and remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in 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-alpha (TNFα) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

b. Risk Benefit Assessment

Moderately to severely active ulcerative colitis (UC) is a serious chronic disease which has a substantial impact on patients' quality of life. There are available treatments for moderate to severe disease; however limitations exist, and many patients are unable to achieve sustained remission while other patients develop intolerance to or side effects from their current treatment regimens. Additional treatment options for patients with moderately to severely active UC, particularly those who have failed prior anti-TNF therapy, is needed.

Review of the Application and considering recommendations from the Advisory Committee, this reviewer believes that the benefit of vedolizumab in adult patients with moderately to severely active ulcerative colitis outweighs the risks associated with the use of the drug product, in patients who have failed immunomodulators, TNFα antagonists, or corticosteroids. The applicant has adequately characterized the potential risk of PML with vedolizumab to support approval and concomitant immunosuppressants should not be limited to a specific duration in clinical practice. Given the potential risk for PML, as well as the risk for serious infections and drug induced liver injury, a post-marketing observational study should be required, as well as enhanced pharmacovigilance in the postmarketing setting. In addition, these risks should be adequately included in the labeling.

Reviewer Comments: On December 9, 2013, the Advisory Committee met and supported the approval of vedolizumab for UC and CD based on the evidence of efficacy and safety. The majority of the AC members agreed that the benefits outweigh the risks to support the approval for the proposed UC population that have failed corticosteroids, as well as immunosuppressants or TNF α-antagonists and commented that restrictions would be burdensome in clinical practice. The committee agreed that concomitant immunosuppressants should not be limited to a specific duration. The review team agreed with the AC recommendations, and this is reflected in the indication and labeling.

c. Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not required for this application because it is believed that the benefits of vedolizumab outweigh the risks for the intended population.

Reviewer Comments: On December 9, 2013, the Advisory Committee met and agreed that the applicant has adequately characterized the potential risk of PML with vedolizumab with the current data to support approval. Members noted that further quantification of this potential risk and continued monitoring and observation are still necessary and stressed that any risk mitigation strategies required beyond labeling to manage the potential risk of PML should not be overly burdensome for prescribers.

On February 3, 2014 the REMS Oversight Committee (ROC) met to discuss whether a REMS should be required for vedolizumab to mitigate the potential risk for PML. Updated exposure data were provided by the applicant through December 27, 2013 which indicated that zero cases of PML have been reported in the vedolizumab clinical development program, out of 3326 subjects exposed. This included 1056 patients who received 24 or more months of vedolizumab, ruling out a risk of PML of 2.8/1000 patients exposed for 24 or more months (with 95% confidence based on the Rule of 3). The review team recommended to the ROC that a REMS was not needed because the benefits of vedolizumab outweigh the risks for the intended population and for the following reasons:

- *UC and CD cause substantial morbidity and decreased quality of life.*
- *Current treatment options do not adequately address medical needs in the subset of UC and CD patients who fail other therapies.*
- *Vedolizumab has robust efficacy as a treatment for UC.*
- *Vedolizumab has a potential risk of PML, as well as risks of hepatotoxicity, serious infections and malignancies. However:*
    - *Vedolizumab has a targeted mechanism of action against the human lymphocyte integrin α4β7 in contrast to Tysabri (α4β1 & α4β7).*
    - *The nonclinical evidence does not support an association between the drug and PML.*
    - *No cases of PML have been identified in the clinical trials.*
    - *The risk of PML has been characterized to an upper bound of 2.8/1000 based on the number patients with 2 or more years of vedolizumab exposure and the fact that no cases of PML have arisen to date.*
- *Labeling is sufficient to mitigate the potential risk of PML based on currently available evidence. Additionally, the Applicant will communicate the potential risk of PML through a Dear Healthcare Professional Letter and Healthcare Professional Brochure. FDA will also publish a Perspectives Piece in the New*

England Journal of Medicine describing the product's benefit-risk assessment and FDA's approval decision for vedolizumab, along with the strategies to address the potential risk of PML. Finally, FDA will hold a Stakeholders Call 1 – 2 weeks following approval. Relevant societies will be invited to participate in this call and the focus will be on the safety of vedolizumab, including the potential risk for PML.

- *A post-marketing observational study and continuation of the ongoing open-label study will help to quantify the risk of PML.*
- *Enhanced pharmacovigilance will help to ensure that if any cases of PML are spontaneously reported in the post-marketing setting, maximal information on these cases will be obtained at the time of the initial report. The need for prompt and complete reporting by prescribers will be further emphasized via the communication strategies mentioned above.*

The committee's opinion was divided on the need for a REMS. Some stated that, based on the current data, the statutory standard for requiring a REMS is not met (because the benefits outweigh the risks), and the ROC did not take the position that a REMS with a communication plan would be the only acceptable approach. The ROC agreed that FDA needs to communicate the potential risk of PML to prescribers to ensure that they will recognize and report cases of PML, if they emerge.

Based on the information provided by the Applicant, and recommendations from the AC and ROC, the review team determined that a REMS is not needed at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

Required Pediatric Assessments:
The pediatric study requirement for ages 0 to < 5 years of age in ulcerative colitis is waived and pediatric study requirements for ages 5 through 17 years are deferred. The required pediatric studies are:

PMR 1: Conduct a dose-ranging trial to determine the PK/PD, safety, and tolerability of vedolizumab in pediatric patients 5 through 17 years with moderately to severely active ulcerative colitis or Crohn's Disease who have failed conventional therapy.

PMR 2: Conduct a randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by vedolizumab in pediatric patients 6 through 17 years with moderately to severely active Crohn's disease who have failed conventional therapy.

PMR 3: Conduct a randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by vedolizumab in pediatric patients 5 through 17 years with moderately to severely active ulcerative colitis who have failed conventional therapy.

In addition, the following Postmarketing Safety Requirements were recommended by the Clinical review team and agreed upon by the Applicant:

PMR 4: Complete Clinical Trial C13008, an open-label trial to determine the long-term safety of vedolizumab in patients with ulcerative colitis and Crohn's disease. Safety evaluations include but are not limited to the occurrence of serious infections including progressive multifocal leukoencephalopathy (PML) and malignancies.

PMR 5: A post-marketing, prospective, observational, cohort study of vedolizumab versus other agents for inflammatory bowel disease. Clearly define recruitment and retention methods a priori. The study's primary outcome is serious infections. Secondary outcomes include, but are not limited to, progressive multifocal leukoencephalopathy (PML), malignancies, specific infections including gastrointestinal and upper respiratory infections, liver toxicity, serious adverse events (SAEs), other clinically significant infections that are not SAEs but are classified as moderate or severe and require antibiotic treatment, infusion-related reactions and adverse reactions. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to vedolizumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in serious infection risk above the comparator background rate, with a pre-specified statistical analysis method. For the vedolizumab-exposed and comparator(s), the study drug initiation period should be clearly defined, including any exclusion and inclusion criteria. Ensure adequate number of patients with at least 24 months of vedolizumab exposure at the end of the study. Provide a final study protocol, agreed upon by FDA, prior to study initiation and a final statistical analysis plan (SAP) allowing FDA adequate time to review and comment. Annually, provide progress updates of study patient accrual and summarize study population demographics. Provide study safety data in periodic safety update reports.

The following post-marketing commitments were also recommended by the clinical team and agreed upon by the Applicant.

PMC 1: Conduct a prospective, observational pregnancy exposure registry study in the United States that compares the pregnancy and fetal outcomes of women exposed to vedolizumab during pregnancy to an unexposed control population or collect vedolizumab pregnancy exposure data by collaborating with an existing disease-based pregnancy registry. Annual interim reports are to be submitted to the Agency.

PMC 2: Conduct a milk-only lactation trial in lactating women receiving vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk using a validated assay in order to appropriately inform the Nursing Mother's subsection of labeling.

Reviewer Comments: While the language of the above listed PMRs and PMCs was agreed upon, final language has not yet been decided on at the time of this review addendum, so finalized language is subject to change. In addition, there were a number of drug quality and clinical pharmacology PMCs which were agreed upon by the sponsor which are not included in this addendum. These can be found in the relevant review discipline reviews and will be included in the action letter.

3. Advisory Committee Summary

A Joint Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee to evaluate the safety and efficacy of intravenous vedolizumab for the induction and maintenance of ulcerative colitis and Crohn's disease and the postmarket risk management strategy was held on December 9, 2013.

The following recommendations and responses were provided by the expert committee, in response to the 4 questions relevant to the ulcerative colitis indication:

- The committee voted 21 to 0 that the applicant adequately characterized the potential risk of PML with vedolizumab to support approval. Members noted that continued quantification of this potential risk and monitoring and observation are still necessary.
- The committee voted 19 to 1, with 1 abstention, that if vedolizumab is approved, concomitant immunosuppressants should not be limited to a specific duration (e.g., during induction only).
- Thirteen (13) of 21 committee members voted that the proposed UC population should include patients that have failed corticosteroids, immunosuppressants, or TNFα-antagonists, while the remaining 8 committee members voted that the proposed indications should require that patients have failed immunosuppressants or TNFα-antagonists only (i.e., failure of corticosteroids only would not be sufficient).
- When asked what post-market risk mitigation strategies beyond labeling, if any, would be needed to ensure that the product's benefits outweigh its risks, the committee members commented that it is important to quantify the PML risks and to monitor other infections in addition to PML. Members stressed that post-market risk mitigation strategies should not be burdensome for the practitioners.

Reviewer Comments: The review team agreed with the committee's recommendations to not limit the use of concomitant immunosuppressants and to include patients who have failed corticosteroids in the indication. The review team also agreed that the applicant adequately characterized the potential risk of PML with vedolizumab to support approval. While the committee did not vote on post-market risk mitigation strategies, members noted that continued quantification of this potential risk, monitoring and observation are still necessary and stressed that any risk mitigation strategies required beyond labeling to manage the potential risk of PML should not be overly burdensome for prescribers.

4. Updated Safety Information: Hepatocellular Injury

As was reported in the original clinical review, there were no imbalances of liver test abnormalities between treatment groups in phase 3 trials of vedolizumab, and there were no clear differences in rates of marked abnormalities of relevant lab parameters, across treatment groups. See Table 1.

Table 1: Marked Abnormalities in Clinical Laboratory Values: C13006 and C13007

Analyte, n(%)	VDZ/PBO N = 279	PBO/PBO N = 297	VDZ/VDZ N = 1434
ALT > 3.0 x ULN	6 (2)	3 (1)	22 (2)
AST > 3.0 x ULN	7 (3)	0	16 (1)
Bilirubin > 2.0 x ULN	2 (<1)	2 (<1)	7 (<1)

Source: Sponsor Submission, Integrated Summary of Safety, Table 18.2.3.1

[a] Marked abnormalities were outside the pre-defined criteria for marked abnormality and had an on-treatment value more extreme than the baseline value

There were, however, several cases of acute hepatocellular injury during the vedolizumab clinical development program. Four (4) patients reported serious adverse events of hepatitis during the controlled and open-label extension study. These adverse events occurred after a range of vedolizumab exposure, from 2 to 35 doses, and covered a spectrum of plausibility in terms of relationship to drug. The case felt to have the highest likelihood of being related to vedolizumab is described below.

A 20-year old male patient from Italy who was in the Maintenance non-ITT vedolizumab Q4W group was hospitalized for acute hepatitis 57 days after his fifth and final dose of vedolizumab. He was diagnosed with UC 7 years before entering the study and had been previously treated with AZA/6-MP, infliximab, mesalamine, and corticosteroids; however, all UC treatments except 5 mg daily prednisone were discontinued before study entry. The patient had normal baseline serum liver tests and received his 1st dose of vedolizumab on (b) (6) with a 5th and final dose on (b) (6) about 3 months later. At that time, he was found to have new elevations of his liver serum transaminases. A liver ultrasound and biopsy one week later showed a pattern compatible with drug-induced hepatitis and/or chronic autoimmune hepatitis with fibrosis, and 7 weeks later on (b) (6) with a further rise of the transaminases and a rising total bilirubin level, he was hospitalized with acute hepatitis. A workup for viral, autoimmune, and liver storage diseases was negative (except for a slight rise in smooth muscle antibodies of 1 in 40). The patient started treatment with IV corticosteroids and was discharged from the hospital a few days later, when lab work was normalizing. Follow up labs from February of the following year were normal. See Table 2. The event was considered by the investigator to be related to study drug.

Table 2: Select Laboratory Results for Patient C13006-28007-605

Date of Result	ALT (IU/L) [RR 10, 40]	AST (IU/L) [RR 10, 40]	Alkaline Phosphatase (IU/L) [RR 32, 92]	Bilirubin, total (mg/dL, [RR 1.20, 0.20] unless otherwise specified
(b) (6)	18	20	73	5.0* µmol/L
	436	305	148	0.50
	622	458	174	1.47
	285	91	116	20* µmol/L
	15	19	134	0.60

Reviewer Comments: Natalizumab is associated with liver injury, including serious drug-induced liver injury, and this is included in the natalizumab label. The mechanism of action for DILI with Tysabri is not fully understood, however treatment with other biologic agents that modulate T cell activity has resulted in a variety of forms of liver injury – one hypothesis is that drugs which affect t-cell migration also could potentially cause liver injury through perturbation of regulatory or suppressor T cells, especially in individuals with pre-existing susceptibility to develop an auto-immune diathesis. There were cases

of liver injury, including serious liver injury with vedolizumab use during the clinical development program, so I will provide you with some of those details. A case of a 20 year old male with UC experiencing acute hepatocellular injury at the time of his 5th dose of vedolizumab seems to have the highest probability of causality related to drug, of the cases seen. Appropriate labeling and careful follow-up, including enhanced pharmacovigilance, and expeditious evaluation of patients in the postmarketing setting will be needed.

5. Ethics and Good Clinical Practices

The Office of Scientific Investigations (OSI) performed site investigations of 4 clinical sites:

Table 3: Clinical Site Inspections

Clinical Site Number	Location	Number of Subjects Screened/Randomized/ Prematurely Discontinued	Site Selection Rationale	Inspection Date	Final Classification
58045	Seattle, WA	24/15/10	Highest US enrollment	09/3/2013 and 10/3/2013	VAI[a]
58156	San Antonio, TX	10/8/4	High efficacy in Induction and Maintenance Trials	10/7 – 10/15/2013	NAI[b]
04006	Leuven, Belgium	49/41/25	Highest overall enrollment	10/21 – 10/29/2013	NAI
12019	Czech Republic	9/9/4	Highest efficacy compared to placebo	11/4 – 11/11/2013	NAI

[a] VAI = Deviation(s) from regulation
[b] NAI = No deviation from regulation

Overview of Inspection Findings:

Clinical Site 58156:
At this US site, for Protocol C13006, a total of 10 subjects were screened, 8 were enrolled and 4 subjects completed the study. An audit of 4 subjects' records was conducted. No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of underreporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site.

Clinical Site 04006:
At this foreign site, for Protocol C13006, a total of 49 subjects were screened, 41 were enrolled and 25 subjects discontinued from the study. An audit of 13 subjects' records was conducted. No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site.

Clinical Site 12019:
At this foreign site, for Protocol C13006, a total of 9 subjects were screened, 9 were enrolled and 7 subjects completed the study. An audit of 9 subjects' records was conducted. No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site.

Clinical Site 58045:
At this US site, for Protocol C13006, a total of 24 subjects were screened, 15 were enrolled and 5 subjects completed the study. An audit of 24 subjects' records was conducted. The adverse events were reported as specified in the protocol and no major transcription errors were observed comparing source with eCRF data. A form 483 was issued for the following violations related to Protocol 13006:

1. No phone calls were made to subjects who enrolled in protocol 13006 and reported PML symptoms to reassure and instruct that they may remain in the study and to confirm that the symptoms have not recurred or persisted. In his response, the CI stated that the calls were made but not documented.
2. A stool sample for the analysis of the Fecal Calprotectin was not collected in 12 out of 24 subjects enrolled in Protocol 13006. In his response, the CI noted this lapse, due to difficulty for subjects to produce stool samples and promised increased communication with the sponsor to mitigate the issue if this type of problem should recur.
3. Pharmacist technician (b) (6) involved in the study drug reconstitution, dose preparation and dispensing is not included in the Site Personnel Signature/Delegation Log for Protocols C13006 and C13007. In his response, the CI attributed this to the blinded/unblinded nature of the IP logs and promised corrective action such that the site will not maintain two separate logs.

Reviewer comment: OSI inspection reports are complete and OSI recommended that data from the inspected sites can be used in support of the BLA. This reviewer agrees with the OSI assessment. Three (3) of 4 sites inspected were classified as NAI. Site 58045 was classified as VAI, for the reasons summarized above. These violations, however, did not adversely affect data integrity or subject safety.

6. Summary and Conclusions

The benefit of vedolizumab in adult patients with moderately to severely active ulcerative colitis outweighs the risks associated with the use of the drug product, in patients who have failed immunomodulators, TNFα antagonists, or corticosteroids. A REMS is not required because it is believed that the benefits of vedolizumab outweigh the risks for the intended population. A postmarketing observational study and enhanced pharmacovigilance, in addition to adequate labeling and communication to prescribers on the potential risk of PML, are adequate at this time.

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/s/

LAURIE B MULDOWNEY
04/11/2014

ANIL K RAJPAL
04/11/2014
I concur with Dr. Muldowney.

To: Dr. Laurie Muldowney, MD; Medical Officer, DGIEP

From: Mark Avigan, MD CM; Associate Director, OPE/OSE

Date; December 6, 2013

Subject: Vedolizumab AC presentation, December 9, 2013

I have been asked to comment briefly on a hepatotoxicity signal that was observed in clinical trials associated with vedolizumab to help prepare for an impending presentation this week by Dr. Muldowney to the AC that is being convened to consider approval of this agent for the treatment of UC and Chrohn's disease. My suggested edits to the planned text for slides 89-97 to be presented at the AC are provided as a follow-up to our discussion. The corresponding edited power points are in the attached slide set.

'Natalizumab is associated with liver injury, including serious drug-induced liver injury, and this is included in the natalizumab label. The mechanism of action for DILI with Tysabri is not fully understood, however treatment with other biologic agents that modulate T cell activity has resulted in a variety of forms of liver injury – one hypothesis is that drugs which affect t-cell migration also could potentially cause liver injury through perturbation of regulatory or suppressor T cells, especially in individuals with pre-existing susceptibility to develop an auto-immune diathesis.

There were cases of liver injury, including serious liver injury with vedolizumab use during the clinical development program, so I will provide you with some of those details.

There were no imbalances of liver test abnormalities between treatment groups in phase 3 trials, and there were also no clear differences in rates of marked abnormalities of relevant lab parameters, between treatment groups (though the numbers were small, so comparisons are limited) during these controlled trials. I do want to highlight a few cases of vedolizumab-associated liver injury, however, which occurred during vedolizumab clinical development.

There were, however several cases of acute hepatocellular injury during the vedolizumab clinical development program.

Specifically, 4 patients reported serious adverse events of hepatitis during the controlled and open-label extension study. These adverse events occurred after a range of vedolizumab exposure, from 2 to 35 doses. All of these patients discontinued study drug and were treated with corticosteroids, and all recovered. There is, of course, a spectrum of plausibility in terms of relationship to drug. I provide some additional details on what we considered to be the most compelling case with the next slide, but wanted to first just give some very high level information on the other 3 cases, which we felt were less likely to be related to vedolizumab, but of course, that can't be ruled out entirely with the information we have.

The most recent case was reported a few weeks ago during the 120-day safety update. This was a 36 year female who developed hepatitis after 35 doses of vedolizumab, so it would be less likely to be *related* to vedolizumab *alone*, first off because of the duration of exposure before experiencing the AE. Subsequently this patient was diagnosed with subacute cutaneous lupus erythematosus, and while her liver tests began normalizing after discontinuation of vedolizumab and introduction of corticosteroids, she was continuing to have some elevations in liver functions several months after discontinuing treatment.

The next case was a 35 year old female who developed hepatitis 41 days after her second dose of vedolizumab, so there is more temporal plausibility here, however, she had started sulfasalazine several months before the trial, and her symptoms with fever, labs with marked eosinophilia, and biopsy results were more consistent with an allergic reaction to sulfasalazine, rather than vedolizumab-induced liver injury. Of course, vedolizumab, as a cause, cannot be entirely ruled out.

The next case was a 23 year old female who developed hepatitis 13 days after her 2nd dose of drug. This case was highly confounded, however, as the patient was hospitalized with pneumonia and a number of medications were started before the event.

The most compelling case was a 20-year old male patient from Italy who experienced acute hepatocellular injury which occurred after his 5th dose of vedolizumab. He was diagnosed with UC 7 years before entering the study and had been previously treated with AZA/6-MP, infliximab, mesalamine, and corticosteroids, however, all UC

treatments except 5 mg daily prednisone were discontinued before study entry. With normal baseline serum liver tests, he received his 1st dose of vedolizumab on [redacted] with a 5th and final dose on [redacted] about 3 months later. At that time, he was found to have new elevations of his liver serum transaminases. He was asymptomatic and the transaminase levels were then monitored on a weekly basis – I didn't include the [redacted] labs on this slide, however, they remained elevated in the same range as the labs 4 days later on [redacted] - A liver biopsy and ultrasound showed a pattern consistent with either drug-induced or autoimmune hepatitis, and 7 weeks later on [redacted] with a further rise of the transaminases and a rising total bilirubin level that reached 20 micromol/liter, near the upper limit of normal, he was hospitalized with acute hepatitis and started treatment with IV corticosteroids.

As you can see, the [redacted] labs were his peak values. He was discharged from the hospital a few days later and his lab work was normalizing. Follow up labs from February of the following year were normal. Based on the information reviewed, this case seems to have the highest probability of causality related to vedolizumab, of the cases seen.

As stated, there were cases of acute hepatocellular injury which occurred with vedolizumab use, one case in particular seemed probably related to drug treatment. There is mechanistic plausibility for such reactions since integrin antagonists have a potential to affect regulatory T cells that should ordinarily prevent autoimmune organ injury. With these findings, appropriate labeling, careful follow-up and expeditious evaluation of patients in the postmarketing setting will be needed.'

Summary Comment:

These cases of acute hepatocellular liver injury associated with vedolizumab, some associated with autoimmune features that responded to de-challenge and prednisone raise a concern that some individuals have increased susceptibility to developing organ damage due to the immunomodulatory effects of this agent, some just after a few doses. The concern is supported by the documentation of similar cases of acute hepatotoxicity associated with natalizumab, a monoclonal agent with very similar

pharmacological/immunological actions (See References below). With these findings, product labeling that highlights that treated patients may develop acute liver injury even after a few doses of vedolizumab which requires patient vigilance, careful clinical follow-up with expeditious & thorough evaluation by the treating physicians with expertise in the diagnosis of liver disorders will be needed. In addition, the sponsor must engage proactively in educating both physicians and patients to both recognize and report all liver injury cases and proactively follow up and assess all cases with a plan to regularly report these to FDA.

References for Natalizumab Hepatotoxicity

Bezabeh, S. et al. Aliment Pharmacol Ther 2010. 31:1028-1035
Lisotti A et. al. *Dig and Liv Dis* 2012;44(4):356-357.

134 Pages Have Been Withheld In Full As A Duplicate Copy Of The Slides From The Joint Meeting Of GIDAC and DSaRM, Dated December 9, 2013 Which Is Located On fda.gov

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/s/

PHONG DO
01/29/2014
Checking into DARRTS for Mark Avigan (Primary Author)

MARK I AVIGAN
01/29/2014

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125507
Priority or Standard	Standard
Submit Date(s)	June 20, 2013
Received Date(s)	June 20, 2013
PDUFA Goal Date	June 20, 2014
Division / Office	Division of Gastroenterology and Inborn Error Products/Office of Drug Evaluation III
Reviewer Name(s)	Klaus Gottlieb, MD, MS, MBA
Review Completion Date	December 29, 2013
Established Name	Vedolizumab
(Proposed) Trade Name	Entyvio
Therapeutic Class	Integrin Receptor Antagonist
Applicant	Takeda
Formulation(s)	Lyophilized powder for injection
Dosing Regimen	300 mg infused intravenously over approximately 30 minutes at 0, 2, and 6 weeks, and then every 8 weeks thereafter
Indication(s)	reducing signs and symptoms, inducing and maintaining clinical response, clinical

	remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist
Intended Population(s)	Adult patients with moderately to severely active Crohn's disease as defined by the CDAI

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer that vedolizumab be approved for the indication of:

Achieving[1] clinical response and remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to steroids or immunomodulators (such as azathioprine, 6-mercaptopurine, or methotrexate) or a tumor necrosis factor-alpha (TNFα) antagonist.

1.2 Risk Benefit Assessment

Moderately to severely active Crohn's disease (CD) is a serious chronic disease which has a substantial impact on patients' quality of life. CD involves chronic inflammation of all layers of the bowel and may affect any segment of the GI tract. For CD, the most common patterns of GI involvement are in descending order, (1) the distal small intestine and colon, (2) the small intestine alone, and (3) the colon alone. Common symptoms of CD are diarrhea, abdominal pain, weight loss, fever, and rectal bleeding.

The inflammation can extend beyond the mucosa and involve the wall of the bowel, leading to the development of strictures (narrowing), fistulae between diseased parts of the bowel and adjacent structures (i.e., bladder, other bowel segments and skin) and abscesses. Perianal manifestations are common. Extraintestinal tissues (skin, eyes and joints) may also be inflamed. In addition, there may be sequelae due to malabsorption (anemia, vitamin deficiency, cholelithiasis, nephrolithiasis or metabolic bone disease).

CD typically has a chronic relapsing course with acute clinical episodes. Some patients, however, have chronic poor health due to active bowel inflammation, fistulae, or other disease-related events. Morbidity may be considerable, particularly for patients whose disease is not controlled by currently available agents. An increased risk of mortality has been reported. (Canavan et al., 2007; Canavan et al., 2007; Wolters et al., 2006) The annual incidence in North America (United States and Canada) is estimated to be between 3.1 and 14.6 cases per 100,000 person-years, with between 10,000 and 47,000 new cases of CD diagnosed annually. It is estimated that over 630,000 people in North America have CD based on a prevalence of 199 cases per 100,000 persons (Loftus 2004).

[1] "Achieving clinical response and remission" is recommended over "inducing and maintaining clinical response" for reasons that will be detailed in the body of the review.

Other treatment options in this population of moderately to severely active CD include corticosteroids, immunomodulators, TNFα-antagonists (infliximab, adalimumab, and certolizumab) and natalizumab. The number of patients that have received natalizumab for CD is very small (approximately 1,100). The natalizumab indication is limited to patients that have failed TNFα-antagonists.

Review of the current Application reveals that the benefit of vedolizumab for reducing signs and symptoms and achieving clinical remission in adult patients with moderately to severely active Crohn's disease who have failed prior therapies has been adequately demonstrated, and the benefit outweighs the risks associated with the use of the drug product.

Induction and Maintenance Studies Results Summary

To support this indication, the applicant submitted two studies (C13007 and C13011) that evaluated vedolizumab 300 mg as therapy for moderate to severe Crohn's disease. Induction was evaluated in two trials; however, evaluation of maintenance was limited to one trial. Study C13007 evaluated both induction and "maintenance". Study C13011 evaluated only induction. In Study C13007 approximately 50% of subjects were naïve to TNFα antagonists and 50% patients had a history of "treatment failure" on TNFα antagonists. In contrast, the primary analysis population in Study C13011 was limited to patients who had failed previous TNFα antagonist therapy. These patients constituted approximately 75% of patients randomized in this trial. An additional 25% of patients in Study C13011 were naïve to TNFα antagonist therapy and were not included in the primary efficacy analysis. The "Maintenance" trial component of Study C13007 randomized vedolizumab-treated patients who had achieved clinical response at Week 6 during the induction phase of Study C13007 to 1 of 2 vedolizumab IV dosing regimens (300 mg Q4W or Q8W) or placebo. Additional patients, who had not been randomized into the induction phase of Study C13007 but who had achieved clinical response during open label treatment with vedolizumab 300 mg (referred to as Cohort 2 patients) were also randomized into the Maintenance phase of Study C13007. In contrast to the total number of patients in the ITT population of the vedoluzimab arm of the Induction phase of Study C13007 (n=220), the total number treated with open label vedolizumab 300 mg in Cohort 2 (to assure adequate patient numbers for randomization into the Maintenance Phase of the trial) was 747.

The following table summarizes the high level efficacy results of Study C13007 and Study C13011. For induction, the primary endpoint was met in the induction phase of Study C13007, but not in study C13011 (induction in TNFα-failure patients). Both primary and first secondary endpoints were met in the maintenance phase of study C13007.

Table 1. Endpoints in CD Studies C13007 and C 13011

Study	C13007 (50% TNFα-failures)		C13011 (75% TNFα- failures)	
Endpoint	**Primary**	**1st secondary**	**Primary**	**1st secondary**
Induction	endpoint met[i]	endpoint not met	endpoint not met	no formal hypothesis testing allowed[j]
Maintenance	endpoint met	endpoint met	n/a	n/a

[i] one of two alternative endpoints met
[j] nominally significant

Therefore, only one clinical trial met the primary endpoint to support the efficacy of vedolizumab for the induction of clinical remission in Crohn's disease. There was only one maintenance trial, and it met the primary endpoint.

Dosing

The applicant's dosing recommendations for vedolizumab are a dose of 300 mg administered as an IV infusion over 30 minutes at Week 0, Week 2, Week 6, and Q8W thereafter. The dosing recommendations go on to state that if clinical response is not achieved by Week 6, or if patients lose response when dosed Q8W, dosing Q4W may be considered.

The dosing recommendations for induction (i.e., dosing at Weeks 0 and 2 in order to achieve clinical remission at Week 6) are supported by data from C13007. However, C13011 suggests that an additional dose at Week 6 is required in order for clinical remission to be achieved at Week 10. This Reviewer recommends that the labeling describe the time course for achieving clinical remission based on the clinical trial data, and that a postmarketing trial be conducted to evaluate induction of clinical remission at Week 10 (see Section 1.4 and see Section 9.2).

In the maintenance phase, vedolizumab was also effective at achieving clinical remission at Week 52 with both the Q4W and the Q8W dosing regimens. Given that neither dosing regimen showed a clear efficacy or safety advantage, it is appropriate to treat with the lowest effective dose (i.e., the Q8W dosing regimen).

The applicant's recommendation to consider dose escalation is based on PK data (vedolizumab trough data and PK modeling from Phase 3 studies) as well as information derived from Studies C13007, C13011, and C13008. An increase in dosing frequency for patients who fail to achieve clinical response by Week 6 was not formally studied as part of the applicant's Phase 3 program (i.e., Studies C13007 and C13011), however, and Study C13007 was not powered to directly compare the Q4W and Q8W doses. Study C13008 was open-label and not designed to assess efficacy endpoints, so efficacy data from this study should be considered with caution. Additional data is required to support the dosing escalation recommendations by the applicant.

Safety

This Reviewer believes vedolizumab has been shown to be safe for its intended use as recommended in the labeling. Overall, the safety profile of vedolizumab was adequately characterized during the clinical development program. See Section 7.

Since 2007, the vedolizumab clinical development program included a Risk Assessment and Minimization for PML (RAMP) program. The RAMP program was thorough, and no cases of PML were identified through the 120 day safety data cutoff. This included 903 patients exposed to 24 or more vedolizumab infusions with 4-weeks of follow up and approximately 80% of whom received prior immunosuppressant therapy. Less than 1% of patients tested positive for JC viremia, and JCV antibody testing was not included in the RAMP program. There were 0 cases of PML identified during the vedolizumab clinical development program to date.

Outstanding Issues

The Applicant adequately demonstrated the efficacy of vedolizumab and that the benefit of vedolizumab outweighs its potential risks for adult patients with moderately to severely active Crohn's disease. Outstanding issues related to vedolizumab include:

- The key safety issue is the potential risk of progressive multifocal leukoencephalopathy (PML). Risk management strategies beyond labeling were discussed at the Advisory Committee on December 9, 2013; the Advisory Committee members commented that it is important to quantify PML risks and to monitor other infections in addition to PML. Members also noted that post-market risk mitigation strategies should not be burdensome for the practitioners. Self-reported adverse events registries could also be considered. The final decision on this issue has not yet been made by the review team. (See Sections 1.3 and 9.3 of this review.)
- Two potential cases of drug related liver injury were reported. Additional information is forthcoming from the Applicant. Enhanced pharmacovigilance in the postmarketing setting may be needed to ensure any future cases are captured.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The primary serious risk of harm relevant to REMS considerations is the potential risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Natalizumab, an integrin antagonist approved in the treatment of multiple sclerosis and Crohn’s disease, is associated with an increased risk for PML. No cases of PML have been reported in the vedolizumab clinical development program, out of 3326 patients exposed, however a theoretical risk remains.

The applicant proposes a REMS with medication guide and communication plan (b) (4) as the risk management strategy for vedolizumab.

A variety of approaches have been utilized by CDER in the past to address PML risk in other drug products, from PML specific labeling to REMS with elements to assure safe use (ETASU). Most of the products using only PML-explicit labeling to manage PML risk are products used in oncology and transplantation medicine, where there may already exist an underlying risk for opportunistic infections and PML. Natalizumab includes PML specific labeling in a Black Box Warning and has a required REMS with ETASU. The REMS requirement for natalizumab was based on the determination that there was a definitive risk for this serious, and often fatal condition in a population previously not at risk.

Given that there have been no cases of PML detected in the vedolizumab clinical development program to date, the risk of PML with vedolizumab remains a theoretical risk. One could argue that labeling alone may be an appropriate strategy. Alternatively, an underlying risk for PML has not been seen in patients with UC and CD on other therapies, excluding natalizumab, and the risk for PML has not been entirely ruled out, with the safety database provided by the sponsor. While nonclinical data is reassuring in demonstrating the selectivity of vedolizumab's binding to the α4β7 integrin, the mechanism by which PML develops in patients administered integrin antagonist products is not completely understood and clinical data is needed to estimate risk.

It is unclear what evidentiary threshold we may be comfortable with, to rule out a specific level of risk of PML in these patients with a reasonable level of certainty. A critical question which will drive the selection of the optimal risk management strategy for vedolizumab is: considering the totality of the non-clinical and clinical evidence, how many vedolizumab patients need to be studied for how long to rule out the risk of PML with a reasonable level of certainty. If it is determined that the Applicant has not ruled out the potential of PML with a reasonable level of certainty, a REMS with ETASU may be needed. This approach will increase the burden on patients, prescribers, pharmacies, and infusion centers, and it is possible that vedolizumab may not address the unmet medical need in CD to the fullest extent possible. It would be important to discontinue the REMS program once a sufficient number of patients have been exposed, assuming no cases of PML arise.

These issues were discussed at the Advisory Committee on December 9, 2013, and are being discussed internally at the time this review was written; a final decision on REMS or risk management strategies beyond labeling has not yet been made by the review team. The Advisory Committee members commented that it is important to quantify PML risks and to monitor other infections in addition to PML. Members also noted that post-market risk mitigation strategies should not be burdensome for the practitioners. Self-reported adverse events registries could also be considered. (See Section 9.3 of this review).

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review, the following Postmarket Requirements and Commitments are recommended:

The Clinical Pharmacology review team recommends the following post marketing commitment (PMC) studies:

- A study to reanalyze banked immunogenicity serum samples from ulcerative colitis trial C13006 and Crohn's disease trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference. This recommendation is based on the finding of inadequate assessment of immunogenicity incidence in the current BLA.
- Evaluate the disease-drug-drug interaction (DDDI) potential between vedolizumab and other CYP substrates. This recommendation is based on the current understanding that CYP enzymes expression is suppressed by inflammatory cytokines associated with inflammatory conditions, and they can normalize upon improvement of the inflammatory conditions. We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of UC or CD, an inflammatory disease condition, on the exposure of CYP substrate drugs (i.e., the disease drug interaction). Such study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the DDDI.

The following study is recommended from the Pediatric and Maternal Health Staff as a PMC:

- Conduct a milk-only lactation trial in lactating women receiving vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk using a validated assay in order to appropriately inform the Nursing Mother's subsection of labeling

The PREA postmarketing requirement (PMR) for CD is described below:

- The applicant has requested a Waiver of Pediatric Study for pediatric patients from birth to (b) (4) and a Deferral of Pediatric Study for pediatric patients (b) (4) to < 18.
- We generally have waived requirements for pediatric studies of CD treatments in children under the age of 6 years due to the low CD incidence in that age group. The final determination of pediatric waiver and deferral will be made upon presentation to the Pediatric Research Committee (PeRC) as part of the review of this BLA for moderately to severely active CD in adults.

This Reviewer recommends the following PMC:

- A randomized controlled trial to evaluate induction of clinical remission at Week 10 after a dose of vedolizumab 300 mg at Weeks 0, 2, and 6.

This Reviewer recommends that a long-term observational safety study should be conducted as a PMR:

- Specifics of the study design such as the duration and number of patients are pending at the time of this review; discussions about details of the study design are currently ongoing with the Office of Surveillance and Epidemiology - Divisions of Pharmacovigilance, Epidemiology, and Risk Management. The applicant has proposed a postmarketing observational study of 5000 patients over 7 years. In addition, this reviewer recommends that "paraesthesias and dysaesthesias" and "skin conditions" should be considered (pending discussion with reviewers in the Office of Surveillance and Epidemiology - Divisions of Pharmacovigilance, Epidemiology, and Risk Management) to be included as adverse events of special interest with targeted neurological and dermatological investigations in the proposed post-marketing observational study to further evaluate and characterize the potential risk of neuropathy and dermopathy with vedolizumab. In addition, this Reviewer recommends that a determination of circulating CD34+ cells (a marker of immaturity) in response to the administration of vedolizumab should be included. Further, this Reviewer recommends ((pending discussion with the CBER immunologist consulted, Dr. Jennifer Reed) that determination of IgA and IgM in nasopharyngeal samples should be included as a substudy in the proposed observational postmarketing study.

2 Introduction and Regulatory Background

2.1 Product Information

Vedolizumab is a humanized IgG1 monoclonal antibody that belongs to the class of integrin antagonist drugs. Vedolizumab specifically targets the human lymphocyte integrin α4β7, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) which is expressed on the endothelium of intestinal vasculature.

Established name:	vedolizumab
Proposed trade name:	Entyvio
Pharmacologic class:	Integrin Receptor Antagonist
Dosage Form and Strength:	lyophilized powder for injection available in sterile single-use vials containing 300 mg vedolizumab for intravenous infusion

Applicant's proposed indication for Crohn's disease:

- Vedolizumab is indicated for reducing signs and symptoms, inducing and maintaining clinical response, clinical remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

Applicants proposed dosing regimen:

- 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently available approved treatments for moderately to severely active CD appear in the table below.

Table 2. Currently Available Treatments (Moderately to Severely Active CD)

Treatment	Drug Class	Indication
Remicade (infliximab)	TNF Antagonist	REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
Humira (adalimumab)	TNF Antagonist	HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
Cimzia (certolizumab)	TNF Antagonist	CIMZIA is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
Tysabri (natalizumab)	Integrin Antagonist	TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α [*see Warnings and Precautions (5.1)*].

2.3 Availability of Proposed Active Ingredient in the United States

Vedolizumab is a new molecular entity (NME) that is not approved or marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Tysabri (natalizumab) is the only currently marketed integrin antagonist. It is approved for inducing and maintaining clinical response and remission in adult patients with moderate to severely active Crohn's Disease (CD) with evidence of inflammation and who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF-α.

Tysabri contains a boxed warning that it increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking Tysabri who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving Tysabri as monotherapy.

As per the current label for Tysabri, three factors that are known to increase the risk of PML in Tysabri-treated patients have been identified:
(1) Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than (b) years of TYSABRI treatment.
(2) Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
(3) Presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.

Because of the risk of PML, Tysabri has a REMS requirement composed of a Medication Guide, Communication Plan, and Elements to Assure Safe Use including prescriber, pharmacy, and patient registration. Tysabri is available only through a special restricted distribution program called the CD Tysabri Outreach Unified Commitment to Health (TOUCH™) program. This program includes infusion site training and maintains a computerized database that captures enrollment, patient tracking, and drug distribution.

In addition to increasing the risk of PML, hypersensitivity reactions, including anaphylaxis, have occurred in patients receiving Tysabri and were more frequent in patients with antibodies to Tysabri. Tysabri may also increase the risk for infections, including urinary tract infection, pneumonia, and gastroenteritis.

At the time of approval for CD, one of the post-marketing commitments (PMCs) was for a prospective observational study (CD INFORM) that specified that at least 2,000 CD patients must be enrolled, and that a least 1,000 patients must have two years of Tysabri treatment. CD INFORM was designed primarily to determine the incidence and pattern of serious and/or clinically significant infections, malignancies, and other serious adverse events (SAEs) in patients with Crohn's disease (CD) treated with natalizumab; the main safety outcome of interest in CD INFORM is PML. At the time of this review, the accrual of the study has been limited by the use of the marketed product in CD, and a total of only 187 subjects have been enrolled. Additional data is not yet available.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical development of vedolizumab began in 1998, and IND 009,125 was opened in June 2000 to initiate clinical development in the United States. In January 2006, development of vedolizumab was placed on clinical hold due to concerns that integrin antagonists might predispose patients to progressive multifocal leukoencephalopathy (PML). This stemmed from the market withdrawal of natalizumab, following 2 cases of

confirmed PML in patients receiving the drug to treat MS and one reported case in a patient treated for Crohn's disease. All integrin antagonists under development in the US at that time were placed on clinical hold. The clinical hold on IND 009,125 was lifted in July 2007 with the implementation of an active screening and monitoring program. Multiple subsequent regulatory meetings, including an Advisory Committee (AC) meeting, have focused on risk minimization and safety monitoring related to potential PML risk.

A Joint Meeting of the Gastrointestinal Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee to evaluate intravenous vedolizumab for treatment of Inflammatory Bowel Disease (induction and maintenance of Crohn's Disease and Ulcerative Colitis) and the risk of PML was held on July 20, 2011. The purpose of this closed session Advisory committee was to seek the committee's recommendations regarding the Phase 3 study design for vedolizumab, including the number of patients and duration of study needed to exclude the risk of PML. The following recommendations and responses were provided by the expert committee, in response to 4 questions:

- The committee voted 12 to 5, with one abstention, that the available nonclinical and human pharmacodynamic data for vedolizumab do not provide assurance of less risk of PML than natalizumab.
- The committee commented on an acceptable safety database size for pre-approval assessment of PML risk in patients with CD and UC. No consensus was reached, however, the AC strongly expressed that the duration of exposure is important and that 24 months could be considered as the minimum duration timeframe. The majority of the committee felt that increasing the sample size has merit.
- The committee voted 15 to 2, with one abstention, that the available nonclinical and clinical data do not support making the entry criteria less stringent for vedolizumab phase 3 studies (i.e., allow entry of patients that have not yet been treated with TNFα antagonists or immunosuppressants).
- The committee voted 17 to 0, with one abstention, that restrictions on concomitant immunosuppressants (prohibited beyond the induction phase of vedolizumab treatment) should not be made less stringent.

Based on the AC recommendations and over the course of several meetings between the sponsor and FDA, the following major agreements were made relating to the risk of PML with this class of therapy:

- patient screening and monitoring: a screening baseline neurologic exam with exclusion of those with abnormal findings, education of site personnel and patients, and updated informed consent documents
- selection criteria: patients enrolled in phase 3 studies were required to meet the stricter requirement of inadequate response or intolerance to immunosuppressants or TNFα antagonists, rather than immunosuppressants, TNFα antagonists, or corticosteroids
- concomitant medications: patients in phase 3 studies were allowed concomitant steroid use for one and one-half years, with tapering at week 6 in patients that

are in clinical response, or when clinical response is achieved. In addition, concomitant immunosuppressant use was allowed for up to 6 weeks in Phase 3 studies, but must be otherwise prohibited.

- safety database: the safety database at the time of original BLA submission must include data on at least 900 patients that received ≥ 24 infusions, with a minimum of 4 weeks of follow-up after the last infusion

It should be noted that the Division only reviewed the US versions of the protocols. Some of the above protocol provisions, most notably restrictions on entry and restrictions on concomitant immunosuppressive therapies, are not part of the protocols outside the US.

Several formal meetings also occurred between the sponsor and FDA to discuss manufacturing changes. Vedolizumab was initially manufactured utilizing a mouse myeloma (NS0) cell line, and initial clinical studies used drug product from this process (MLN02, Process A). A Chinese hamster ovary (CHO) cell line was developed to improve productivity, and drug product from this process (MLN0002, Process B) was used in multiple Phase 1 and 2 clinical studies. Further manufacturing improvements to the CHO-based process were then implemented to establish a commercially representative process (MLN0002, Process C) that was used to supply Phase 3 clinical trials. A PK/PD comparability study was completed prior to initiating Phase 3 studies, to compare Process B and C products. For simplicity, vedolizumab will be used throughout this review to refer to the drug product throughout its development.

Presubmission regulatory activities related to this submission included an advisory committee meeting and 14 formal face-to-face meetings between the sponsor and FDA. In addition, there were a number of teleconferences and written correspondences exchanged during the development program for Crohn's disease. The sponsor was granted Fast Track Designation in February 2013. Table 1 below summarizes pre-submission regulatory meetings and submissions and highlights key clinical agreements.

Table 3 Pre-submission Regulatory History

Date	Regulatory Action(s)
June 7, 2000	Original IND 9125 submitted for MLN02
June 2004	Type C Meeting to discuss the clinical development outcomes from two Phase 2 studies, M200-021 and L299-016.
January 24, 2006	IND 9125 placed on clinical hold for insufficient information to allow the Agency to assess the risk of progressive multifocal leukoencephalopathy (PML) to subjects with MLN02
April 4, 2006	Type A Meeting to discuss options for removing clinical hold, including PML risk minimization and safety monitoring.
July 26, 2006	Type C Meeting to discuss manufacturing changes from MLN02 to MLN0002
June 18, 2007	Sponsor submitted an amendment which was a complete response to the clinical hold and included the Risk Assessment and Minimization of PML (RAMP) program.
July19, 2007	Removal of clinical hold based on additional safety measures related to potential PML risk
December 11, 2007	Type C Meeting to continue discussions about PML risk management program
April 18, 2008	Type C meeting to discuss overall development plan for MLN0002, specifically dose selection, CMC, and nonclinical data to support Phase 3 studies.
June 5, 2008	Type C, End of Phase 2 Meeting to discuss pivotal studies for the proposed IBD indications
September 16, 2008	Type B, End of Phase 2 meeting to discuss the CMC development plan
September 26, 2008	Type C End of Phase 2 Teleconference to discuss outstanding clinical questions and issues for Phase 3 activities..
September 10, 2009	Type C, Phase 3 meeting to discuss the Statistical Analysis Plan for the Phase 3 Crohn's disease study, C13007
July 13, 2010	Meeting to discuss Phase 3 development plan
July 20, 2011	Closed Joint Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee
September 6, 2011	Type C follow-up Meeting to discuss the outcomes from the Joint GIDAC/DSaRM meeting
July 24-25, 2012	Type C, post-Phase 3 meeting to discuss pivotal study data and clinical plan to support registration
November 6, 2012	Type C, Pre-BLA meeting to discuss clinical, nonclinical, and regulatory aspects of the BLA
November 13, 2012	Type B, Pre-BLA meeting to discuss CMC aspects of the BLA
February 21, 2013	Fast track designation granted for vedolizumab in the treatment of ulcerative colitis and Crohn's disease

2.6 Other Relevant Background Information

There is no other relevant background information, other than that discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity are acceptable. The electronic application was well-organized and easily navigable.

The Office of Scientific Investigations (OSI) is scheduled to perform site investigations of 4 clinical sites:

Table 4 Clinical Site Inspections

Clinical Site Number	Location	Number of Subjects Screened/Randomized/Prematurely Discontinued	Site Selection Rationale
58045	Seattle, WA	24/15/10	Highest US enrollment
58156	San Antonio, TX	10/8/4	High efficacy in Induction and Maintenance Trials
04006	Leuven, Belgium	49/41/25	Highest overall enrollment
12019	Czech Republic	9/9/4	Highest efficacy compared to placebo

OSI inspection reports are pending at the time of this review.

3.2 Compliance with Good Clinical Practices

There was a statement of Good Clinical Practice. "Each of the clinical studies was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulatory requirements."

The application also included a debarment certification that the applicant did not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

The sponsor provided a single signed copy of FDA Form 3454 with an appended list of investigator names from each covered study. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as

defined in 21 CFR 54.2(a). No FDA Form 3455s were provided, as no investigators reported financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Vedolizumab is recombinant humanized IgG_1 monoclonal antibody composed of two light chains of the kappa subclass and two heavy chains linked together by two disulfide bridges to form a Y-shaped molecule.

Figure 1: Schematic diagram of vedolizumab

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Vedolizumab is produced in CHO cells and has a molecular weight of approximately 147 kDa (b) (4) (b) (4) (b) (4) During product development, several manufacturing changes were implemented. These resulted in 3 different iterations of the product (process A, B, and C). Significant changes included:

- Changing the host cell line from NS0 to CHO to improve productivity and the product quality profile
- (b) (4) production scale (commercialization scale)

The impact of these changes was assessed through a variety of biochemical, biophysical, immunological, and pharmacological assessment, and the results support the comparability of vedolizumab across these processes. Process A was [redacted] was studied in phase 1 and phase 2 trials. Process B was [redacted] and process C is a lyophilized formulation for infusion or injection. Bioequivalence between Processes B and C was demonstrated in healthy subjects in Study C13009.

The drug product is a sterile, lyophilized formulation which contains histidine/histidine [redacted] arginine HCl, sucrose, and polysorbate 80. Each single-use vial provides 300 mg vedolizumab and is reconstituted with 4.8 mL Sterile Water for Injection. The reconstituted drug product is then diluted into 0.9% sodium chloride to an approximate volume of 250 mL.

There are no major efficacy or safety issues from chemistry, which recommends approval. For more information see the Product Quality Review.

4.2 Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because vedolizumab is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical assessment of vedolizumab included pharmacology, pharmacokinetics, acute IV toxicology in monkeys, repeated dose IV toxicology in monkeys and rabbits, reproductive toxicology, and local tolerance studies. In addition, special nonclinical studies were completed in order to compare the impact of vedolizumab and natalizumab on immunotoxicity and CNS immune surveillance.

In Vitro Pharmacology

Comparative binding affinity of vedolizumab for the α4β7 integrin was determined in competitive binding assays using peripheral blood lymphocytes of Cynomolgus monkey and human whole blood. These studies demonstrated that the binding affinities of vedolizumab for either B or memory CD4 lymphocytes appeared to be similar in Cynomolgus monkeys and humans. In vitro studies utilizing human and murine cell lines selectively expressing specific integrins demonstrated the specificity of vedolizumab for binding to the α4β7 integrin and not α4β1 or αEβ7 integrin. The selectivity of vedolizumab for inhibition of α4β7-mediated cell adhesion interactions was also examined and showed that vedolizumab inhibited α4β7-MAdCAM-1 and fibronectin and did not inhibit α4β7-VCAM-1, α4β1-VCAM-1, or α4β1-fibronectin-mediated adhesive interactions.

In vitro studies also demonstrated that vedolizumab did not mediate antibody dependent cell-mediated cytotoxicity or complement dependent cytotoxicity in human peripheral blood mononuclear cells. In addition, vedolizumab did not induce T lymphocyte activation or cytokine release. Tissue cross-reactivity studies were conducted using a panel of monkey and human tissues, and no unanticipated tissue cross reactivity was observed.

In Vivo Pharmacology

An animal efficacy study was conducted in Tamarin monkeys with naturally occurring chronic colitis using ACT-1 (murine homologue of vedolizumab). ACT-1 treatment resulted in resolution of diarrhea in all animals by Day 3 and colonic mucosal biopsies on Day 5 showed ACT-1 localization to the $\alpha4\beta7^+$ lymphocytes in the lamina propria. Biopsy results also revealed reduced mucosal density of $\alpha4\beta7^+$ lymphocytes from Day 5 to Day 20. Control animals had no clinical or immunohistologic improvement.

Toxicology

Toxicity studies were conducted in Cynomolgus monkeys. Lymphoplasmacytic gastritis was observed in both MLN0002 and control monkeys in a 26-week study, though MLN0002 treated monkeys had greater regeneration of superficial mucosal epithelium in response to this gastritis. The significance of this is not known. *Balantidium coli* (parasites) were observed in the cecum and colon of both control and vedolizumab treated monkeys, and no dose response in vedolizumab treated monkeys was observed.

In a 3-month toxicity study of New Zealand white rabbits, no differences were noted between control animals and those treated with vedolizumab. A reproduction study in pregnant New Zealand white rabbits showed no evidence of impaired fertility or harm to the fetus with vedolizumab administration on gestation day 7 at single IV doses up to 100 mg/kg. Similarly, a pre and postnatal development study with vedolizumab in monkeys showed no evidence of any adverse effect on pre and postnatal development at IV doses up to 100 mg/kg.

Special Nonclinical Studies

A decrease in immune surveillance of the CNS by T-lymphocytes is hypothesized to contribute to the development of PML. The sponsor conducted a study using an Experimental Autoimmune Encephalomyelitis (EAE) model in Rhesus monkeys (a model of multiple sclerosis; there is no animal model of PML) to assess the impact of vedolizumab and natalizumab on CNS immune surveillance. The results of this study showed that while natalizumab appeared to inhibit immune surveillance of the CNS, vedolizumab had no such effect.

In addition, a 3-week comparative immunotoxicity study of natalizumab and vedolizumab was completed in Cynomolgus monkeys. Natalizumab caused a

significant increase in lymphocyte populations (e.g., b-lymphocytes, t-helper lymphocytes, etc.), whereas there was no change in these populations in vedolizumab-treated monkeys.

There are no major efficacy or safety issues from nonclinical, which recommends approval. For more information see the Nonclinical Review by Tamal Chakraborti.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team found the information submitted to support this BLA to be acceptable with the following recommendations for post marketing commitment (PMC) studies:

- A study to reanalyze banked immunogenicity serum samples from ulcerative colitis trial C13006 and Crohn's disease trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference. This recommendation is based on the finding of inadequate assessment of immunogenicity incidence in the current BLA.
- Evaluate the disease-drug-drug interaction (DDDI) potential between vedolizumab and other CYP substrates. This recommendation is based on the current understanding that CYP enzymes expression is suppressed by inflammatory cytokines associated with inflammatory conditions, and they can normalize upon improvement of the inflammatory conditions. We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of UC or CD, an inflammatory disease condition, on the exposure of CYP substrate drugs (i.e., the disease drug interaction). Such study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the DDDI.

Additional summary information from the clinical pharmacology review is provided below. For more detailed information see the Clinical Pharmacology Review by Lanyan Fang, PhD, Yow-Ming Wang, PhD, Justin Earp, PhD, Nitin Mehrotra PhD, Sarah Dorff, PhD, and Michael Pacanowski, PharmD.

4.4.1 Mechanism of Action

Vedolizumab is a recombinant humanized IgG1 antibody which selectively binds α4β7 integrin, a glycoprotein on the surface of leukocytes which are involved in GI mucosal immunity. Vedolizumab blocks the interaction of human lymphocyte integrin α4β7 with its ligand, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of intestinal vasculature. This inhibits the migration of

these leukocytes into the GI mucosa and thus decreases the inflammation associated with CD.

4.4.2 Pharmacodynamics

Study C13002 assessed the relationship between vedolizumab serum concentrations and the extent of α4β7 binding saturation in three dose cohorts (2, 6, and 10 mg/kg). Subjects received a total of 4 vedolizumab doses administered at Days 1, 14, 29, and 85. Maximum binding saturation (i.e., near 100% inhibition of MAdCAM-1-Fc binding to α4β7) occurred within one hour of vedolizumab administration at all dose levels, suggesting that maximum inhibition of α4β7 is unrelated to dose. Maximum inhibition persisted throughout treatment until 84, 126, and 112 days after the last dose for the 2, 6, and 10 mg/kg dose cohorts, respectively. The significance of the saturation of the α4β7 receptor is only one factor related to drug efficacy. These results suggest that near-maximum α4β7 binding will be maintained with the recommended dosing regimen of 300 mg Q8W.

4.4.3 Pharmacokinetics

Vedolizumab exhibits target-mediated drug disposition leading to decreased clearance with increasing doses, due to target saturation. However, the exposure was approximately dose-proportional over the dose range of 2 to 10 mg/kg, following repeated dose administration in CD patients. The mean apparent terminal half-life was approximately 25 days at 300 mg dose. The population PK analysis showed disease severity, body weight, serum albumin, age, prior TNFα antagonist therapy, and concomitant medications had no clinically meaningful impact on PK.

The clinical pharmacology assessment found the proposed dosing regimen (i.e., 300 mg at Weeks 0, 2, 6 and Q8W thereafter) acceptable based on exposure response data. The exposure response analysis in Study C13007 was based on the ITT population, where the trough concentration was used as the exposure variable and clinical remission or enhanced clinical response at each of the timepoints (Weeks 6 and 52) were used as the primary response variables. No exposure-response relationships were evident between clinical remission or enhanced clinical response at either Week 6 or Week 52 and vedolizumab trough concentrations. The lack of exposure-response relationship at Week 52 is consistent with the lack of dose-response observed between the Q4W and Q8W dosing regimens at Week 52.

4.4.4 Immunogenicity

The immunogenicity of vedolizumab could not be reliably assessed during clinical development due to drug interference in the immunogenicity assay. The drug tolerance level of the immunogenicity assay (500 ng/mL) was significantly less than the mean vedolizumab steady state trough concentrations during clinical trials, so the incidence of ADA were likely to be underestimated during treatment. For example, 4% of patients who received continuous vedolizumab in Studies C13006 and C13007 developed anti-

drug antibodies at any time during treatment; however, 17% of patients who received vedolizumab during induction but placebo during the maintenance phase had ADAs at Week 52, when drug levels were undetectable. Since ADAs could degrade during this time period, 17% may still be an underestimation of the true immunogenicity rate. There were 8 patients with persistently positive ADA, and none of these patients achieved clinical remission at Weeks 6 or 52 in controlled trials. Seven of these subjects had available drug concentration data which showed undetectable vedolizumab concentrations in 5 patients and reduced vedolizumab concentrations in 2 patients.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Status, Study Dates, No. of Centers	Study Design	Primary Objective[a]	Dose, Regimen, and Route of Administration[b]	Subject Population	No. of Subjects Dosed
Study C13007: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Crohn's Disease					
Completed, 23 Dec 2008-08 May 2012, 285 centers (see information submitted for non-IND foreign sites according to CFR 312.120)	Randomized, placebo-controlled, double-blind study This pivotal trial included 2 complete studies: one to evaluate the effects of induction therapy and one to evaluate the effects of maintenance therapy. Each of the studies has separate and distinct study endpoints, randomization schema, defined populations, and analysis plans.	Induction: • To determine the effect of vedolizumab induction treatment on clinical remission at 6 weeks • To determine the effect of vedolizumab induction treatment on enhanced clinical response at 6 weeks Maintenance: To determine the effect of vedolizumab maintenance treatment on clinical remission at 52 weeks	Induction: Vedolizumab 300 mg vs. Placebo at Weeks 0 and 2 Maintenance: Vedolizumab 300 mg Q4W or Q8W/dummy vs placebo from Weeks 6-50 IV infusion	Males or females aged18-80 years and CDAI score of 220-450 points; before Amendment 5/6, maximum CDAI was 480. Previous TNFα antagonist exposure limited to 50% of total study population	Induction: • 967 vedolizumab • 148 placebo Maintenance: • 660 vedolizumab Q4W • 154 vedolizumab Q8W • 301 placebo

Status, Study Dates, No. of Centers	Study Design	Primary Objective[a]	Dose, Regimen, and Route of Administration[b]	Subject Population	No. of Subjects Dosed
(see information submitted for non-IND foreign sites according to CFR 312.120)	study	therapy (TNFα antagonist failure subpopulation)		demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance to immunomodulators and/or TNFα antagonists. Patients outside of the US may have also been enrolled on the basis of prior corticosteroid treatment failure or intolerance.	

Status, Study Dates, No. of Centers	Study Design	Primary Objective[a]	Dose, Regimen, and Route of Administration[b]	Subject Population	No. of Subjects Dosed
Uncontrolled Efficacy and Safety Studies – Crohn's Disease					
Study C13008: A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients with Ulcerative Colitis and Crohn's Disease					
Ongoing, 22 May 2009-Data cutoff 14 March 2013, 292 centers (see information submitted for non-IND foreign sites according to CFR 312.120)	Open-label, long-term study	To determine the safety profile of long-term vedolizumab treatment	Vedolizumab 300 mg Q4W IV infusion	Male and female patients with moderate to severe UC or CD, aged 18-80 years, who received previous treatment in Studies C13004, C13006, C13007, or C13011 that, in the opinion of the investigator, was well tolerated. Patients who participated in Study C13011 must have completed the Week 10 assessments in that study. In addition, UC and CD patients without previous treatment with vedolizumab (de novo patients) were enrolled directly into this study starting in May 2012.	2243 vedolizumab • 1349 patients with CD • 894 patients with UC

Status, Study Dates, No. of Centers	Study Design	Primary Objective[a]	Dose, Regimen, and Route of Administration[b]	Subject Population	No. of Subjects Dosed
Study C13004: A Phase 2, Multiple Dose, Open-Label Study to Determine the Long Term Safety of MLN0002 in Patients with Ulcerative Colitis and Crohn's Disease					
Completed, 07 Dec 2007-31 Mar 2010, 14 centers (see information submitted for non-IND foreign sites according to CFR 312.120)	Open-label, long-term study	• To provide patients who completed Study C13002 and nonrollover patients with UC and CD the opportunity to receive vedolizumab treatment • To obtain data regarding the long-term safety of vedolizumab treatment	Vedolizumab 2.0 or 6.0 mg/kg (6.0 or 10.0 mg/kg before Amendment 1) on Days 1, 15, 43, then Q8W IV infusion	Males or females aged 18-75 years with UC or CD symptoms of a minimum of 2 months' duration in conjunction with endoscopic and/or histopathologic documentation consistent with UC or endoscopic, radiologic and/or histopathologic documentation consistent with CD that had been obtained within 36 months of screening. Partial Mayo score of 2-7 (UC) or CDAI score of 220-450 (CD) with known UC involvement extending proximal to the rectum or CD involvement of the ileum and/or colon.	• 37 vedolizumab 2.0 mg/kg • 35 vedolizumab 6.0 mg/kg • 19 patients with CD • 53 patients with UC

5.2 Review Strategy

The review of efficacy focuses on the placebo-controlled trial C13007 (induction and maintenance) and C13011 (induction in a population with 75% TNFα failures).

5.3 Discussion of Individual Studies/Clinical Trials

The studies are discussed in detail in section 6. Here we will review inclusion/exclusion criteria and demographics.

C13007 Inclusion/Exclusion Criteria

The study design of C13007 permitted double-blind placebo-controlled comparisons of safety parameters in the both the Induction Study and the Maintenance Study. Enrollment of the additional cohort of patients in the Induction Phase was to increase the number of patients contributing to the induction safety evaluations. In the Maintenance Phase, safety treatment comparisons could be made on all enrolled patients for the entire duration of the study (up to 52 weeks), as even patients initially treated with placebo and those who were non-responders to vedolizumab were to continue into the Maintenance Phase. Additional measures were to be taken to collect safety parameters in these patients beyond the 52-week duration of the trial. Patients who completed or withdrew from the Maintenance Phase may have been eligible for entry into a long-term safety study, C13008. Patients who did not participate in Study C13008 were to have a final visit 16 weeks after their final dose of study drug, and have safety information collected for up to 2 years after the study.

As vedolizumab-treated patients who did not achieve induction response were to be retained in the study after Week 6, the response to additional vedolizumab treatment could be evaluated in exploratory analyses, using a placebo group comparison.

The entry criteria were to ensure that patients who were appropriate for pharmacologic treatment, as assessed by severity of disease, were enrolled into the study. Entry criteria were also to exclude patients who might not benefit from drug or who might be at risk for treatment toxicities. Additional measures to ensure the safety of enrolled patients were to include protocol-mandated criteria for withdrawal in patients who had worsening of disease or required rescue medication. Thus, the protocol ensured that patients who could be treated with placebo (inactive treatment) up to 52 weeks were withdrawn from the study if they experienced treatment failure.

Detailed information was to be collected on prior treatments for CD, and patient response to prior treatments, including protocol-specified definitions for the type of treatment failure. Thus, both the efficacy and safety of vedolizumab could be assessed in the important subgroups of patients who were TNFα antagonist naïve and those who had prior treatment failure with these agents.

Selection of Study Population

Inclusion criteria were selected to ensure that patients appropriate for treatment with biologic therapy were enrolled. Importantly, criteria were chosen to select for patients with moderately to severely active CD and to exclude patients who were too ill or who could not benefit from medical treatment (such as patients with symptomatic stenoses, patients with severe disease that required surgical treatment, and patients with extensive surgeries). Patients with serious comorbidities or who had neurological conditions that could confound the assessments for potential cases of PML were also to be excluded.

Inclusion Criteria

Each patient must have met all of the following inclusion criteria to be enrolled in the study:

1. Age 18 to 80 years
2. Male or female patient who is voluntarily able to give informed consent
3. Female patients who:
    - Are post-menopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 6 months after the last dose of study drug, OR
    - agree to completely abstain from heterosexual intercourse.

    Male patients, even if surgically sterilized (ie, status post-vasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
    - Agree to completely abstain from heterosexual intercourse.
4. Diagnosis of CD established at least 3 months prior to enrollment by clinical and endoscopic evidence and corroborated by a histopathology report. Cases of CD established at least 6 months prior to enrollment for which a histopathology report is not available will be considered based on the weight of the evidence supporting the diagnosis and excluding other potential diagnoses, and must be discussed with the sponsor on a case-by-case basis prior to enrollment. (Prior to Amendment 5/6, the diagnosis of CD was to have been established for at least 6 months prior to enrollment)
5. Moderately to severely active CD as determined by a CDAI score of 220 to 450 (Prior to Amendment 5/6, the CDAI maximum for enrollment was 480) within 7 days prior to the first dose of study drug **and** 1 of the following:
    - CRP level > 2.87 mg/L during the Screening period ***OR***
    - Ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous cm of intestine) consistent with CD, within 4 months prior to randomization ***OR***
    - Fecal calprotectin 250 mcg/g stool during the Screening period in conjunction with computed tomography (CT) enterography, magnetic resonance (MR) enterography, contrast-enhanced small bowel radiography, or wireless capsule

endoscopy revealing Crohn's ulcerations (aphthae not sufficient), within 4 months prior to screening. (Patients with evidence of fixed stenosis or small bowel stenosis with prestenotic dilation should not be included.)

6. CD involvement of the ileum and/or colon, at a minimum
7. Patients with extensive colitis or pancolitis of > 8 years' duration or limited colitis of > 12 years' duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of enrollment (may be performed during screening).
8. Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up-to- date on colorectal cancer surveillance (may be performed during screening)
9. Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:
   - Immunomodulators
     - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-MP (≥ 0.75 mg/kg) OR
     - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of methotrexate (≥ 12.5 mg/week) OR
     - History of intolerance of at least 1 immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, TPMT genetic mutation, infection)

   - TNF α- antagonists
     - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of 1 of the following agents
     - Infliximab: 5 mg/kg IV, 2 doses at least 2 weeks apart
     - Adalimumab: one 80 mg SC dose followed by one 40 mg dose at least 2 weeks apart
     - Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart ***OR***
     - Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) ***OR***
     - History of intolerance of at least 1 TNFα antagonist (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

   ONLY APPLICABLE TO PATIENTS OUTSIDE THE US (who may have been enrolled on the basis of corticosteroid treatment history):
   - Corticosteroids
     - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or IV for 1 week, ***OR***
     - Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions, ***OR***
     - History of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia,and infection).
10. May be receiving a therapeutic dose of the following drugs:
    a. Oral 5-ASA compounds provided that the dose has been stable for the 2 weeks immediately prior to enrollment.

b. Oral corticosteroid therapy (prednisone at a stable dose $\leq$ 30 mg/day, budesonide at a stable dose $\leq$ 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to enrollment if corticosteroids have just been initiated, or for the 2 weeks immediately prior to enrollment if corticosteroids are being tapered
c. Probiotics (eg, Culturelle, Saccharomyces boulardii) provided that the dose has been stable for the 2 weeks immediately prior to enrollment
d. Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea
e. Azathioprine or 6-MP (for patients participating in the US, only permitted for Cohort 1 patients) provided that the dose has been stable for the 8 weeks immediately prior to enrollment
f. Methotrexate (for patients participating in the US, only permitted for Cohort 1 patients) provided that the dose has been stable for the 8 weeks immediately prior to enrollment
g. Antibiotics used for the treatment of CD (ie, ciprofloxacin, metronidazole) provided that the dose has been stable for the 2 weeks immediately prior to enrollment…

Exclusion Criteria

The exclusion criteria were divided into 3 categories: GI exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Patients meeting any of the following exclusion criteria were not to be enrolled in the study.

Gastrointestinal Exclusion Criteria

1. Evidence of abdominal abscess at the initial screening visit
2. Extensive colonic resection, subtotal or total colectomy
3. History of > 3 small bowel resections or diagnosis of short bowel syndrome
4. Have received tube feeding, defined formula diets, or parenteral alimentation within 21 days prior to the administration of the first dose of study drug
5. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
6. Within 30 days prior to enrollment, have received any of the following for the treatment of underlying disease:
   a. Non-biologic therapies (eg, cyclosporine, thalidomide) other than those listed in the inclusion criteria above
   b. A non-biologic investigational therapy
   c. An approved non-biologic therapy in an investigational protocol
   d. Adalimumab
7. Within 60 days prior to enrollment, have received any of the following:
   a. Infliximab
   b. Certolizumab pegol
   c. Any other investigational or approved biological agent, other than local injections for non IBD conditions (eg, intra-ocular injections for the treatment of wet macular degeneration)
8. Any prior exposure to natalizumab, efalizumab, or rituximab

9. Use of topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks of the administration of the first dose of study drug
10. Evidence of or treatment for *C. difficile* infection or other intestinal pathogen within 28 days prior to enrollment
11. Currently require or are anticipated to require surgical intervention for CD during the study
12. History or evidence of adenomatous colonic polyps that have not been removed
13. History or evidence of colonic mucosal dysplasia
14. Diagnosis of UC or indeterminate colitis

Infectious Disease Exclusion Criteria

1. Chronic hepatitis B or C infection
2. Active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following: Any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation)
    a. History of TB
    b. A positive diagnostic TB test within 1 month of enrollment defined as:
        i. a positive QuantiFERON® test or 2 successive indeterminate QuantiFERON® tests ***OR***
        ii. a tuberculin skin test reaction > 10 mm (> 5 mm in patients receiving the equivalent of > 15 mg/day prednisone).
    c. Chest X-ray within 3 months of enrollment in which active or latent pulmonary TB cannot be excluded
3. Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine
4. Clinically significant extraintestinal infection (eg, pneumonia, pyelonephritis) within 30 days of the initial screening visit

General Exclusion Criteria

1. Previous exposure to vedolizumab
2. Female patients who are lactating or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 prior to study drug administration.
3. Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
4. Any surgical procedure requiring general anesthesia within 30 days prior to enrollment or is planning to undergo major surgery during the study period
5. Any history of malignancy, except for the following: (a) adequately-treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to enrollment. Patients with remote history of malignancy (eg, > 10 years since completion of curative therapy without

recurrence) could have been considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to enrollment.

Demographics C13007 Induction

Overall, baseline demographic characteristics were similar for the treatment groups in the Induction Study ITT Population. In the overall population, there was a higher proportion of female patients than male patients (53% vs. 47%). Most patients were White (89%) and non-Hispanic (96%). The median age was 34.0 years; most patients were < 35 years of age (52%) and few patients were ≥ 65 years (2%). The median body weight was 66.2 kg and the median body mass index (BMI) was 22.9 kg/m^2. With respect to geographic distribution, 36% were enrolled at sites in North America, including 24% from sites in the US, and 64% were enrolled at sites outside of North America, including 23% at Western/Northern European sites, 19% at Central European sites, 14% at sites located Asia, Australia, and Africa, and 8% in Eastern European sites.

The demographic characteristics of the open-label vedolizumab group were generally similar to those observed in the Induction Study ITT Population, except that the open-label vedolizumab group had more patients enrolling at sites in Western/Northern Europe and fewer patients entering at sites in Asia/Australia/Africa and Eastern Europe than was observed for the Induction Study ITT Population.

Baseline Crohn's Disease Characteristics C13007 Induction

Baseline (Week 0) CD characteristics of the Induction Phase Safety Population are summarized by treatment group in the table below. Consistent with the study's inclusion criteria, patients with moderately to severely active CD were enrolled, as demonstrated by the baseline disease characteristics of the treatment groups. The mean duration of disease was 9.0 years (median 7.0 years) and the mean baseline disease activity, as assessed by the baseline CDAI score, was 323.6. Baseline CDAI scores were > 330 in 44% of the patients. The majority of patients had a baseline CRP > 10 mg/L (53%), a baseline fecal calprotectin > 500 µg/g (56%), and disease involvement of both the ileum and colon (55%). A history of prior surgery for CD was reported for 42% of patients. The majority of the patients had no history of fistulizing disease (63%); 15% of the patients had a draining fistula at baseline. Extraintestinal manifestations of the disease were present at baseline in 62% of patients; 82% of patients had a history of extraintestinal manifestations. Most patients had never smoked or were former smokers (73%).The baseline disease characteristics of the treatment groups in the Induction Study ITT Population were generally comparable, although the vedolizumab group had greater proportions of patients with CD duration of ≥ 7 years (50%) and with a history of prior surgery for CD (45%) compared to the placebo group (43% and 36%, respectively). The baseline disease characteristics of the open-label vedolizumab group were generally similar to those observed in the Induction Study ITT Population.

Table 5 Baseline Disease Characteristics C13007 Induction	PLA N = 148	VDZ N = 220	VDZ N = 747	VDZ N = 967	Total N = 1115
Duration of CD (yrs)[c]					
Mean (Std Dev)	8.2 (7.80)	9.2 (8.18)	9.2 (7.63)	9.2 (7.76)	9.0 (7.77)
Median	6.1	7.1	7.2	7.2	7.0
Minimum, maximum	0.3, 42.0	0.5, 43.6	0.2, 42.5	0.2, 43.6	0.2, 43.6
Duration of CD - categorical, n (%)					
< 1 year	12 (8)	12 (5)	45 (6)	57 (6)	69 (6)
≥ 1 - < 3 years	27 (18)	48 (22)	126 (17)	174 (18)	201 (18)
≥ 3 - < 7 years	45 (30)	49 (22)	191 (26)	240 (25)	285 (26)
> 7 years	64 (43)	111 (50)	385 (52)	496 (51)	560 (50)
Baseline disease activity – CDAI[d]					
n	147	219	743	962	1109
Mean (Std Dev)	324.6 (78.08)	327.3 (70.67)	322.2 (67.17)	323.4 (67.98)	323.6 (69.37)
Median	319.0	324.0	320.0	321.0	321.0
Minimum, maximum	155, 584	132, 500	93, 548	93, 548	93, 584
Baseline disease activity – categorical, n (%)					
CDAI ≤ 330	81 (55)	119 (54)	418 (56)	537 (56)	618 (55)
CDAI > 330	66 (45)	100 (45)	325 (44)	425 (44)	491 (44)
Missing	1	1	4	5	6
Baseline CRP (mg/L)					
n	147	220	747	967	1114
Mean (Std Dev)	23.6 (27.85)	24.1 (27.23)	20.4 (27.40)	21.2 (27.39)	21.5 (27.45)

Demographics C13007 Maintenance

In the Maintenance Study ITT Population, the demographic characteristics were generally similar among the treatment groups, except for geographic region. With respect to geographic distribution, greater proportions of patients in the vedolizumab Q8W and Q4W groups were enrolled at sites in North America (38% and 31%, respectively) compared with the placebo group (24%), whereas a greater proportion of placebo patients were enrolled at sites in Western/Northern Europe (35%) compared with the vedolizumab Q8W and Q4W groups (19% and 25%, respectively).
The demographic characteristics of the all vedolizumab combined group were generally consistent with those observed in the Maintenance Study ITT Population, including the greatest proportion of patients enrolling from sites in North America (39%). In addition, the demographic characteristics of the non-ITT vedolizumab patients (Week 6 non-responders) were consistent with those of the Maintenance Study ITT Population (Week 6 responders).

No statistically significant differences were noted between the treatment groups for selected baseline demographic characteristics including gender, race, age, and body

weight. Although the treatment groups differed with respect to the proportions of patients enrolled by geographic site; this difference was not statistically significant.

Baseline Crohn's Disease Characteristics C13007 Maintenance

The baseline disease characteristics were generally similar among the treatment groups in the Maintenance Study ITT Population and indicated moderately to severely active CD present in this population. Although the majority of patients in each of the treatment groups had baseline CDAI scores ≥ 330, the incidence was highest in the vedolizumab Q8W group (62%), followed by the placebo (56%) and the vedolizumab Q4W (51%) groups. The proportions of patients who had both ileal and colonic involvement was highest in the vedolizumab Q8W (64%) group, followed by the placebo (59%) and the vedolizumab Q4W (47%) groups.

The disease characteristics at baseline for the all vedolizumab combined group and the non-ITT placebo group were generally comparable to those of the Maintenance Study ITT Population, with the exception of higher mean baseline values for CRP. Disease characteristics of the non-ITT vedolizumab patients (Week 6 non-responders) were consistent with greater disease severity including longer disease duration and history of prior CD surgery, and greater disease activity with increased CRP and an increased proportion of patients who had previously failed TNFα antagonist therapy, when compared with the Maintenance Study ITT Population.

Table 6 Baseline Crohn's Disease Characteristics C13007 Maintenance

	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
Disease Characteristic	**PLA N = 153**	**VDZ Q8W N = 154**	**VDZ Q4W N = 154**	**PLA[b] (from Week 0) N = 148**	**VDZ Q4W[c] (Week 6 Nonresponders) N = 506**	**PLA N = 301**	**VDZ N = 814**
Duration of Crohn's disease (yrs)[d]							
Mean (Std Dev)	9.6 (8.85)	8.4 (7.28)	7.7 (6.78)	8.2 (7.80)	9.7 (7.77)	8.9 (8.37)	9.1 (7.54)
Median	7.0	6.5	6.4	6.1	8.0	6.3	7.2
Minimum, maximum	0.3, 43.6	0.3, 34.7	0.2, 42.5	0.3, 42.0	0.3, 42.8	0.3, 43.6	0.2, 42.8
Duration of Crohn's disease - categorical, n (%)							
< 1 year	12 (8)	11 (7)	10 (6)	12 (8)	24 (5)	24 (8)	45 (6)
≥ 1 - < 3 years	27 (18)	32 (21)	39 (25)	27 (18)	76 (15)	54 (18)	147 (18)
≥ 3 - < 7 years	37 (24)	39 (25)	31 (20)	45 (30)	133 (26)	82 (27)	203 (25)
≥ 7 years	77 (50)	72 (47)	74 (48)	64 (43)	273 (54)	141 (47)	419 (51)
Baseline disease activity - CDAI[e]							
n	153	153	153	147	503	300	809
Mean (Std Dev)	325.2 (65.58)	325.5 (68.76)	317.0 (65.99)	324.6 (78.08)	324.2 (69.13)	324.9 (71.86)	323.1 (68.46)
Median	315.0	322.0	316.0	319.0	322.0	317.5	322.0
Minimum, maximum	166, 500	149, 486	132, 548	155, 584	93, 517	155, 584	93, 548
Baseline disease activity – categorical, n (%)							
CDAI ≤ 330	86 (56)	78 (51)	96 (62)	81 (55)	277 (55)	167 (55)	451 (55)
CDAI > 330	67 (44)	75 (49)	57 (37)	66 (45)	226 (45)	133 (44)	358 (44)
Missing	0	1	1	1	3	1	5
Baseline CRP (mg/L)							

Disease Characteristic	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA[b] (from Week 0) N = 148	VDZ Q4W[c] (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
n	153	154	154	147	506	300	814
Mean (Std Dev)	17.2 (21.86)	17.9 (29.47)	16.9 (18.68)	23.6 (27.85)	24.8 (29.93)	20.3 (25.14)	22.0 (28.26)
Median	9.8	8.6	9.8	13.7	14.0	12.7	10.6
Minimum, maximum	0.2, 165.0	0.2, 295.0	0.2, 118.0	0.2, 159.0	0.2, 234.0	0.2, 165.0	0.2, 295.0
Baseline CRP - categorical, n (%)							
≤ 2.87 mg/L	24 (16)	35 (23)	25 (16)	20 (14)	83 (16)	44 (15)	143 (18)
> 2.87 - ≤ 5 mg/L	23 (15)	15 (10)	20 (13)	14 (9)	42 (8)	37 (12)	77 (9)
> 5 - ≤ 10 mg/L	32 (21)	39 (25)	35 (23)	28 (19)	92 (18)	60 (20)	166 (20)
> 10 mg/L	74 (48)	65 (42)	74 (48)	85 (57)	289 (57)	159 (53)	428 (53)
Missing	0	0	0	1	0	1	0
Baseline fecal calprotectin							
n	150	148	148	142	483	292	779
Mean (Std Dev)	1142.5 (1429.34)	1044.6 (1502.03)	1219.3 (1784.00)	1421.2 (2076.11)	1314.7 (2123.14)	1278.0 (1775.96)	1245.3 (1957.32)
Median	683.7	583.5	776.3	652.6	702.0	662.1	689.4
Minimum, maximum	23.8, 7581.3	23.8, 9479.0	23.8, 11978.8	23.8, 12429.0	23.8, 18607.5	23.8, 12429.0	23.8, 18607.5
Baseline fecal calprotectin – categorical, n (%)							
≤ 250 µg/g	38 (25)	48 (31)	35 (23)	34 (23)	131 (26)	72 (24)	214 (26)
> 250 - ≤ 500 µg/g	30 (20)	22 (14)	14 (9)	27 (18)	71 (14)	57 (19)	107 (13)
> 500 µg/g	82 (54)	78 (51)	99 (64)	81 (55)	281 (56)	163 (54)	458 (56)

Disease Characteristic	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA[b] (from Week 0) N = 148	VDZ Q4W[c] (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Missing	3	6	6	6	23	9	35
Disease localization, n (%)							
Ileum only	19 (12)	29 (19)	34 (22)	21 (14)	78 (15)	40 (13)	141 (17)
Colon only	43 (28)	27 (18)	47 (31)	43 (29)	156 (31)	86 (29)	230 (28)
Ileocolonic (both ileum and colon)	91 (59)	98 (64)	73 (47)	84 (57)	272 (54)	175 (58)	443 (54)
Other (extra ileum, extra colon)	0	0	0	0	0	0	0
History of prior surgery for Crohn's disease, n (%)	57 (37)	57 (37)	61 (40)	54 (36)	237 (47)	111 (37)	355 (44)
History of fistulizing disease, n (%)	57 (37)	47 (31)	49 (32)	56 (38)	201 (40)	113 (38)	297 (36)
Draining fistula at baseline, n (%)							
Yes	18 (12)	17 (11)	22 (14)	23 (16)	85 (17)	41 (14)	124 (15)
All closed	2 (1)	1 (< 1)	0	2 (1)	6 (1)	4 (1)	7 (< 1)
No fistula at baseline	133 (87)	136 (88)	132 (86)	123 (83)	415 (82)	256 (85)	683 (84)
Smoking status, n (%)							
Current smoker	48 (31)	48 (31)	39 (25)	34 (23)	129 (25)	82 (27)	216 (27)
Nonsmoker (never smoked)	64 (42)	74 (48)	77 (50)	85 (57)	256 (51)	149 (50)	407 (50)
Former smoker	41 (27)	31 (20)	38 (25)	29 (20)	121 (24)	70 (23)	190 (23)
Missing	0	1	0	0	0	0	1

Disease Characteristic	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA[b] (from Week 0) N = 148	VDZ Q4W[c] (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Baseline extraintestinal manifestations, n (%)	95 (62)	87 (56)	91 (59)	107 (72)	316 (62)	202 (67)	494 (61)
History of extraintestinal manifestations, n (%)	125 (82)	124 (81)	124 (81)	123 (83)	423 (84)	248 (82)	671 (82)

Source: Table 14.1.1.6AM.

Abbreviations: CDAI = Crohn's Disease Activity Index; CRP= C-reactive protein; ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; Std Dev = standard deviation; VDZ = vedolizumab.

Baseline refers to Week 0.

a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT Population at Week 6.

b Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.

c Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

d Duration of Crohn's Disease is defined as (1 + first dose date - diagnosis date)/ 365.25.

e Baseline disease activity represents the baseline CDAI score.

C13011 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were generally similar between studies C13007 and C13011 with the exception that this study enrolled primarily TNFα-failure patients defined as follows:

-Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of 1 of the following agents:

- Infliximab: 5 mg/kg IV, 2 doses at least 2 weeks apart
- Adalimumab: one 80-mg subcutaneous (SC) dose, followed by one 40-mg dose, at least 2 weeks apart
- Certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart, OR
- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), OR
- History of intolerance of at least 1 TNFα antagonist (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, and/or infection).

Demographics of C13011

Baseline demographic characteristics were generally similar between the treatment groups in the Overall ITT Population. Among all patients, there was a higher proportion of female patients than male patients (57% vs. 43%). Most patients were White and non-Hispanic. The mean age was 37.9 years; most patients were ≥ 35 years of age (54%) and few patients were ≥ 65 years (2%). More placebo-treated patients (51%) than vedolizumab-treated patients (42%) were ≥35 years. The mean body weight was 70.4 kg and the mean body mass index (BMI) was 24.3 kg/m^2. With respect to geographic distribution, 28% were enrolled at sites in the US and 72% were enrolled at sites outside of the US, including 21% at Central European sites, 19% at Canadian sites, 18% at Western/Northern European sites, 8% at sites located in Asia, Australia, and Africa, and 6% at Eastern European sites.

The demographic characteristics of the TNFα Antagonist Failure ITT Subpopulation were similar to those observed for the Overall ITT Population, except that the difference between the treatment groups in patients < 35 years of age was less pronounced (placebo 46%; vedolizumab 41%). In addition, the TNFα Antagonist Failure ITT Subpopulation had greater proportions of patients enrolled at sites in North America and smaller proportions of patients enrolled at sites in Central Europe than the Overall ITT Population.

Baseline Crohn's Disease Characteristics C13011 Induction

Consistent with the study's inclusion criteria, patients with moderately to severely active CD were enrolled, as demonstrated by the baseline disease characteristics of the treatment groups. In the Overall ITT Population, the mean duration of disease was 10.3 years, with the majority of the patients having been diagnosed for ≥7 years (57%). The mean baseline disease activity, as assessed by the baseline CDAI score, was

statistically significantly higher in the vedolizumab group (313.9) than the placebo group (301.3), with 37% of vedolizumab-treated patients having a baseline CDAI score > 330 compared with 29% of the placebo-treated patients. The majority of the patients had a baseline CRP > 10 mg/L (50%), a baseline fecal calprotectin > 500 µg/g (58%), and disease involvement of both the ileum and colon (61%). A history of prior surgery for CD was reported for 44% of the patients. The majority of the patients in both treatment groups had no history of fistulizing disease, and only 12% of the patients had a draining fistula at baseline. Extraintestinal manifestations of the disease were present at baseline in 59% of the patients. Most patients in both treatment groups had never smoked or were former smokers (70%). The baseline CD characteristics of the TNFα Antagonist Failure ITT Subpopulation were similar to those observed for the Overall ITT Population, except for disease duration and baseline CDAI score. The mean duration of disease was somewhat longer in the TNFα Antagonist Failure ITT Subpopulation, with 64% of the patients having been diagnosed for ≥ 7 years. The statistically significant difference between the treatment groups for mean baseline CDAI score observed in the Overall ITT Population was marginally significant in the TNF αAntagonist Failure ITT Subpopulation (306.1 placebo; 316.1 vedolizumab).

Table 7 CD Baseline Characteristics in C13007

Baseline Crohn's Disease Characteristics – TNFα Antagonist Failure ITT Subpopulation and Overall ITT Population

Crohn's Disease (CD) Characteristic	TNFα Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
Duration of CD (yrs)a						
Mean (Std Dev)	11.5 (8.09)	11.6 (8.64)	11.6 (8.36)	10.0 (7.98)	10.6 (8.75)	10.3 (8.37)
Median	9.6	9.4	9.5	8.0	8.4	8.0
Min, Max	1.0, 42.9	0.5, 41.8	0.5, 42.9	0.3, 42.9	0.3, 41.8	0.3, 42.9
Duration of CD – categorical, n (%)						
< 1 year	1 (< 1)	2 (1)	3 (< 1)	12 (6)	11 (5)	23 (6)

Crohn's Disease (CD) Characteristic	TNFα Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
≥ 1 - < 3 years	12 (8)	17 (11)	29 (9)	25 (12)	28 (13)	53 (13)
≥ 3 - < 7 years	39 (25)	42 (27)	81 (26)	52 (25)	52 (25)	104 (25)
≥ 7 years	105 (67)	97 (61)	202 (64)	118 (57)	118 (56)	236 (57)
Baseline disease activity – CDAIb						
Mean (Std Dev)	306.1 (55.43)	316.1 (52.63)	311.1 (54.19)	301.3 (54.97)	313.9 (53.17)	307.7 (54.38)
Median	301.0	317.0	311.0	298.0	313.0	304.0
Min, Max	166, 564	196, 524	166, 564	166, 564	196, 524	166, 564
Baseline disease activity – categorical, n (%)						
CDAI ≤ 330	107 (68)	99 (63)	206 (65)	148 (71)	132 (63)	280 (67)
CDAI > 330	50 (32)	59 (37)	109 (35)	59 (29)	77 (37)	136 (33)
Baseline CRP (mg/L)						
Mean (Std Dev)	18.8 (23.58)	20.7 (24.70)	19.8 (24.13)	18.5 (21.98)	19.0 (23.17)	18.8 (22.56)
Median	9.4	10.1	9.7	10.5	9.7	9.8
Min, Max	0.2, 118.0	0.2, 168.0	0.2, 168.0	0.2, 118.0	0.2, 168.0	0.2, 168.0
Baseline CRP – categorical, n (%)						
≤ 2.87 mg/L	34 (22)	31 (20)	65 (21)	41 (20)	46 (22)	87 (21)
> 2.87 to ≤ 5 mg/L	16 (10)	11 (7)	27 (9)	19 (9)	14 (7)	33 (8)
> 5 to ≤ 10 mg/L	31 (20)	37 (23)	68 (22)	42 (20)	48 (23)	90 (22)
> 10 mg/L	76 (48)	79 (50)	155 (49)	105 (51)	101 (48)	206 (50)
Baseline fecal calprotectin (µg/g)						
N	157	154	311	206	204	410
Mean (Std Dev)	1459.5 (2475.01)	1249.2 (2071.60)	1355.3 (2282.93)	1426.5 (2357.76)	1148.1 (1878.58)	1288.0 (2134.79)
Median	647.0	693.6	658.0	665.4	618.3	656.8
Min, Max	23.8, 20000.0	23.8, 20000.0	23.8, 20000.0	23.8, 20000.0	23.8, 20000.0	23.8, 20000.0
Baseline fecal calprotectin categorical, n (%)						
≤ 250 µg/g	42 (27)	37 (23)	79 (25)	47 (23)	52 (25)	99 (24)

Crohn's Disease (CD) Characteristic	TNFα Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
> 250 to ≤ 500 µg/g	23 (15)	26 (16)	49 (16)	35 (17)	35 (17)	70 (17)
> 500 µg/g	92 (59)	91 (58)	183 (58)	124 (60)	117 (57)	241 (58)
Missing	0	4	4	1	5	6
Disease localization, n (%)						
Ileum only	20 (13)	21 (13)	41 (13)	29 (14)	33 (16)	62 (15)
Colon only	40 (25)	40 (25)	80 (25)	52 (25)	48 (23)	100 (24)
Ileocolonic (both ileum and colon)	97 (62)	97 (61)	194 (62)	126 (61)	128 (61)	254 (61)
Other (extra ileum, extra colon)	0	0	0	0	0	0
History of prior surgery for CD, n (%)	80 (51)	73 (46)	153 (49)	89 (43)	92 (44)	181 (44)
Smoking status, n (%)						
Current smoker	47 (30)	45 (28)	92 (29)	58 (28)	65 (31)	123 (30)
Never smoked	77 (49)	75 (47)	152 (48)	102 (49)	93 (44)	195 (47)
Former smoker	33 (21)	38 (24)	71 (23)	47 (23)	51 (24)	98 (24)
History of fistulizing disease, n (%)	67 (43)	57 (36)	124 (39)	77 (37)	71 (34)	148 (36)
Draining fistula at baseline, n (%)						

Yes	18 (11)	19 (12)	37 (12)	25 (12)	25 (12)	50 (12)
All closed	0	(< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
No fistula	139 (89)	138 (87)	277 (88)	182 (88)	183 (88)	365 (88)
Extraintestinal manifestations at baseline, n (%)	103 (66)	85 (54)	188 (60)	130 (63)	116 (56)	246 (59)

Source: Table 14.1.1.6AT, Table 14.1.1.6A.

Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ITT = intent-to-treat; Max = maximum; Min = minimum; PLA = placebo; Std Dev = standard deviation; TNFα = tumor necrosis factor alpha; VDZ = vedolizumab.

a Duration of CD is defined as (1+first dose date – diagnosis date)/365.25. b

Baseline disease activity represents the baseline CDAI score.

6 Review of Efficacy

Efficacy Summary

There were two alternative primary endpoints (meeting either one sufficient to declare success) for the induction part of Study C13007 in Crohn's disease: (a) Clinical Remission (CDAI ≤ 150); and (b) Enhanced Clinical Response (CDAI decrease by ≥ 100). The applicant met endpoint (a) but not (b). The absolute effect size over placebo for induction of remission was modest, 7.7 %. In the maintenance of clinical remission part of Study C13007, effect sizes were considerably larger (see table below).

Study C13011 was conducted to investigate the efficacy of vedolizumab in patients who had previously failed TNFα-antagonists. The total population consisted of 75 % TNFα-failures and 25 % TNFα-naïve patients. The primary analysis population was the 75% who failed TNFα agents. The primary endpoint (achieving clinical remission at Week 6 in the TNF failure population) was not met, however, there was a trend and the total population showed remission rates that exceeded those of placebo by a nominal p of ≤ 0.05.

Table 8 - Efficacy Summary C13007

Clinical Remission at Week 6 in Crohn's Disease (C13007)		
Clinical Remission	Placebo	Vedolizumab 300 mg
N	148	220
Number (%)	10 (6.8 %)	32 (14.5%)
95% CI	(2.7, 10.8)	(9.9, 19.2)
Difference from placebo		7.8%
95% CI for difference from placebo		(1.2, 14.3)
P value for difference from placebo		0.0206

Clinical Remission at Week 52 in Crohn's Disease (C13007)			
Clinical Remission	Placebo	Vedolizumab300 mgQ8W	Vedolizumab300 mgQ4W
N	153	154	154
Number (%)	33 (21.6)	60 (39.0)	56 (36.4)
95% CI	(15.1, 28.1)	(31.3, 46.7)	(28.8, 44.0)
Difference from placebo		17.4	14.7
95% CI for difference from placebo		(7.3, 27.5)	(4.6, 24.7)
P value for difference from placebo		0.0007	0.0042

Based on blinded results from Study C13007, the sponsor hypothesized that a third induction dose or longer duration of dosing could increase the rate of clinical remission measured at 10 weeks. Therefore, an additional dose and increased length of assessment were chosen for evaluation as part of the secondary endpoints in Study C13011, which allowed for evaluation of remission at the Week 10 time point as a planned (pre-specified) secondary endpoint. However, given that the primary endpoint was not reached and sequential testing was prespecified to control the type I error rate, these results are considered exploratory in nature.

Remission rates were higher (with nominally significant p-values) compared with placebo at Week 10 following a third dose of vedolizumab in patients who failed TNFα antagonists. Similar results were seen in the overall population in Study C13011, i.e., the treatment difference between vedolizumab and placebo was greater with vedolizumab at Week 6 and the difference increased at Week 10 following a third infusion.

When reviewing the data of studies C13007 and C13011 in their totality it appears that the ability of vedolizumab to reduce remission in treatment-experienced patients with active CD including those who have failed several TNFα antagonists, is reasonably well supported. The Induction Study of C13007 met 1 of the 2 alternative primary endpoints (clinical remission at Week 6, $p = 0.0206$) and demonstrated a statistically significant treatment difference by application of the prespecified Hochberg method, which requires a p-value of < 0.025 in 1 primary endpoint if the other primary endpoint is > 0.05 (as was the case for the endpoint of enhanced clinical response at Week 6).

The second pivotal study, C13011, demonstrated numerical improvement (not statistical significance) of the primary endpoint of clinical remission at Week 6 in patients who had failed TNFα antagonist therapy and, according to statistical convention, secondary analyses became exploratory. Greater proportions of patients receiving vedolizumab compared to placebo were observed for the predefined secondary endpoints of clinical remission at Week 6 in the overall population (patients who failed TNFα antagonists and patients naïve to TNFα antagonists) as well as in TNFα antagonist failures at Week 10 in Study C13011. By Week 10, the broad population and the 2 major subpopulations that had failed conventional therapy (patients who failed TNFα antagonists and/or immunosuppressants/corticosteroids) achieved improvement in remission and enhanced clinical response.

This reviewer agrees with the applicant that the data suggest that for the population of patients who have failed TNFα antagonists it takes longer to achieve a treatment effect. The increased treatment differences from placebo at Week 10 compared to results at Week 6 in both the population who failed TNFα antagonists and the overall population suggest that an additional dose of vedolizumab and/or more time may be needed to induce remission in some patients. The applicant argues that pharmacologic inhibition of lymphocyte migration to the gut (the presumptive mode of action of vedolizumab) may require a longer timeframe for optimal induction in CD, where the inflammatory process is transmural as compared to UC where the inflammation is more superficial.

Results of the maintenance phase of Study C13007 showed that patients on vedolizumab who had shown a clinical response in the induction phase (decrease of CDAI by 70 points at week 6) had statistically higher rates of being in remission at week 52 than placebo patients. However, results for durable clinical remission (clinical remission in ≥ 80% of study visits) were not significant for the q 8 week dosing interval. A claim for “maintenance” may therefore be problematic; this reviewer recommends that the labeling avoid this term, instead describing the clinical trial findings (see Section 9.2).

The secondary endpoint of "corticosteroid-free remission" was met for the Q8W arm. "Corticosteroid-free remission" was defined as the proportion of patients that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52 (in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at Week 6) (corticosteroid tapering began as soon as a clinical response was achieved). Also, in an exploratory analysis, the applicant showed that with respect to corticosteroids, a greater percentage of patients treated with vedolizumab compared to placebo were in remission at Week 52 and had been off corticosteroids for at least 90 and at least 180 days.

The data of the maintenance phase of C13007 appeared internally consistent as demonstrated across efficacy endpoints in multiple predefined subgroup analyses according to demographic factors, disease activity and previous treatments for CD for maintenance. No single site contributed more than 5% of patients and thus could not contribute disproportionately to the observed treatment effects. Approximately 21% of patients in the C13007 Maintenance Study were enrolled at sites in the US and internal consistency regarding effectiveness across different geographical areas was demonstrated in subgroup analyses.

6.1 Indication

Vedolizumab is intended for the treatment of ulcerative colitis and Crohn’s Disease. This review is limited to the proposed Crohn’s disease indication: “ENTYVIO (vedolizumab) is indicated for reducing signs and symptoms, inducing and maintaining clinical response and remission, and achieving corticosteroid-free remission in adult patients

with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist."

6.1.1 Methods

Two Phase 3 studies were conducted to demonstrate the efficacy and safety of vedolizumab for the treatment of patients with moderately to severely active CD. The efficacy of 300 mg of vedolizumab for the induction *and* maintenance treatment of patients with moderately to severely active CD was evaluated in Study C13007, a Phase 3, multinational, randomized, double-blind, placebo-controlled trial.

A second Phase 3, multinational, randomized, placebo-controlled, double-blind induction study (Study C13011) was conducted in patients with moderately to severely active CD 75 % of which had failed[2]TNF α antagonist therapy while 25 % were naïve to TNFα antagonist therapy.

Crohn's Disease: Induction and Maintenance Study Design of C13007 and C13011

Study C13007: Study C13007 for Crohn's was identical in design to UC Study C13006. As with Study C13006, the Induction and Maintenance Studies within Study C13007 were powered separately and had distinct patient populations, endpoints, and statistical analyses. The primary and ordered secondary induction and maintenance endpoints for Study C13007 are presented in the table which follows. The 2 separate primary endpoints for Study C13007 were not specified or analyzed as co-primary; instead, each one of the two endpoints was evaluated on its own merits and efficacy could be demonstrated if both endpoints were met or just one of the two ("Alternative Primary Endpoints"). The Hochberg method was used to control the Type I error rate.

Figure 2 is an overview of the general study design previously discussed in section 5.

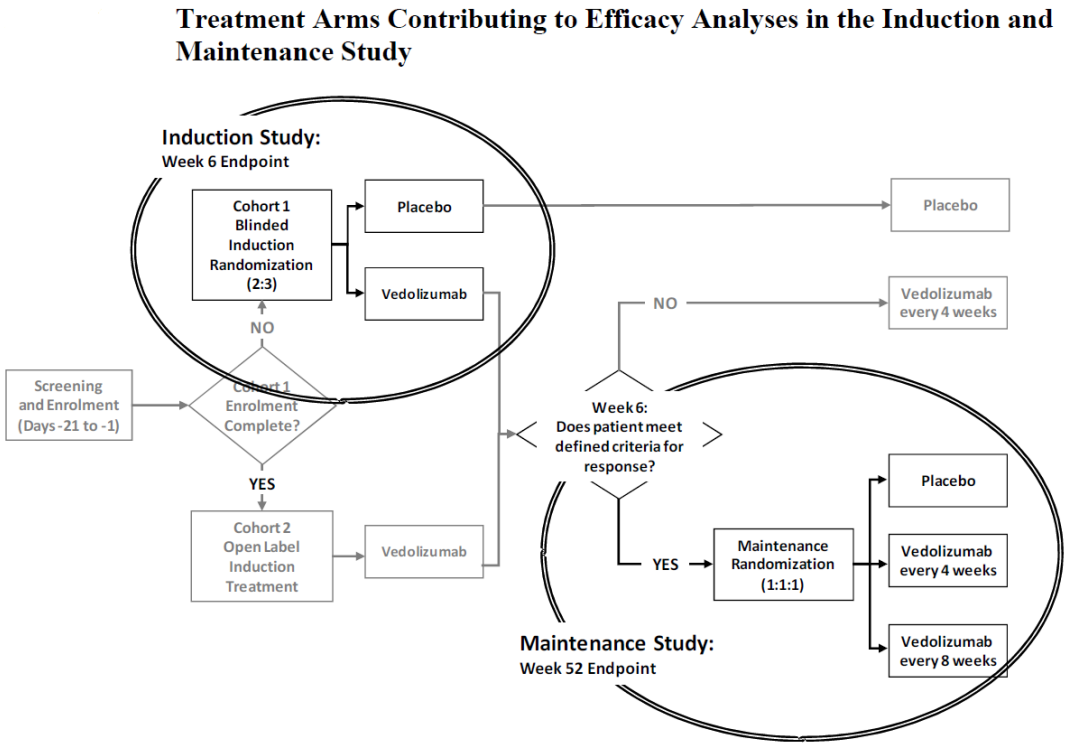
[2] Were intolerant to or had failed TNFα antagonist therapy

Table 9 Endpoints in C13007[3]

Induction Endpoint	Definition
Primary Efficacy Endpoints:	
• Clinical remission at Week 6	CDAI ≤ 150 points.
• Enhanced clinical response at Week 6	≥ 100-point decrease in CDAI from baseline (Week 0).
Ordered Secondary Efficacy Endpoint:	
• Change in C-reactive protein (CRP) levels at Week 6	Change in CRP levels from baseline (Week 0) in patients with elevated CRP at baseline.
Maintenance Endpoint	**Definition**
Primary Efficacy Endpoint:	
• Clinical remission at Week 52	CDAI of ≤ 150 points.
Ordered Secondary Efficacy Endpoints:	
• Enhanced clinical response at Week 52	≥ 100-point decrease in CDAI from baseline (Week 0).
• Corticosteroid-free remission	Patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.
• Durable clinical remission	Clinical remission ≥ at 80% of study visits for an individual patient, including final visit (Week 52).

[3] Sponsor's Table 4-2 Vedolizumab Clinical Overview p. 41

Figure 2 General Outline of the Organization of C13007



Study C13011: Study C13011 was a double-blind, placebo-controlled trial designed to evaluate vedolizumab induction therapy in CD patients who had previously failed one or more therapies including (but not limited to) TNFα antagonists (defined as inadequate response, loss of response, or intolerance). The study population included 75% TNF-α-antagonist-failure patients and 25% TNFα antagonist-naïve patients. Patients were randomized 1:1 to 300 mg vedolizumab or placebo at Weeks 0, 2, and 6, and efficacy was assessed at Weeks 6 and 10. The definitions of clinical remission and enhanced clinical response were the same as those used in Study C13007.

The primary analysis population was patients who had previously failed TNFα antagonist therapy. The primary and ordered secondary induction endpoints for Study C13011 are presented in Table 10**Error! Reference source not found.**.

Table 10 Endpoints in C13011[4]

Induction Endpoint	Definition
Primary Efficacy Endpoint:	
• Clinical remission at Week 6 (TNFα antagonist-failure population)	CDAI ≤ 150 points.
Ordered Secondary Endpoints:	
• Clinical remission at Week 6 (entire study population)	CDAI ≤ 150 points.
• Clinical remission at Week 10 (TNFα antagonist-failure population and entire study population)	CDAI ≤ 150 points.
• Sustained clinical remission (TNFα antagonist-failure population and entire study population)	Clinical remission at both Weeks 6 and 10.
• Enhanced clinical response at Week 6 (TNFα antagonist-failure population)	≥ 100-point decrease in CDAI from baseline (Week 0).

6.1.2 Demographics

Please refer to section 5.3

6.1.3 Subject Disposition

C13007 – Induction Phase

In the Induction Study ITT Population, a total of 23 patients (8 placebo; 15 vedolizumab) had at least 1 unmet entry criterion. The most common deviations were failure to meet the inclusion criterion for baseline CDAI score of 220 to 450 with either a CRP level > 2.87 mg/L, a minimum of 3 nonanastomotic ulcerations or 10 aphthous ulcerations consistent with CD, or a fecal calprotectin > 250 µg/g with appropriate imaging (3 placebo; 4 vedolizumab); CD diagnosis of at least 3 months confirmed by histology or of at least 6 months based on other supporting evidence if histology report not available (0 placebo; 4 vedolizumab); and inadequate or lost response/intolerance of steroids, immunomodulators, and/or TNFα antagonists (1 placebo; 3 vedolizumab). An additional 63 patients in the open label vedolizumab group had violations of inclusion/exclusion criteria, primarily failure to meet the inclusion criterion for baseline CDAI score. No notable trends were observed for the treatment groups with respect to inclusion/exclusion criteria deviations.

In the Maintenance Study ITT Population, a total of 32 patients (8 placebo, 12 vedolizumab Q8W, and 12 vedolizumab Q4W) failed to meet at least 1 study entry criterion. The most common deviations across the treatment groups were failure to meet the inclusion criteria for baseline CDAI score of 220 to 450, with either a CRP level > 2.87 mg/L, a minimum of 3 non-anastomotic ulcerations or 10 aphthous ulcerations consistent with CD, or a fecal calprotectin > 250 µg/g with appropriate imaging (placebo

[4] Sponsor's Table 4-3 Vedolizumab Clinical Overview p. 42

2%; vedolizumab Q8W 4%; vedolizumab Q4W 2%); inadequate or lost response/intolerance of steroids, immunomodulators, and/or TNFα antagonists (placebo < 1%; vedolizumab Q8W 1%; vedolizumab Q4W 3%); and met the exclusion criterion of *C. difficile* infection or other intestinal pathogen within 28 days of study entry (placebo 1%; vedolizumab Q8W 1%; vedolizumab Q4W 3%).

All of the inclusion or exclusion criteria deviations occurred in ≤ 2% of the all vedolizumab combined group, as well as the non-ITT placebo group.
There were few dropouts of any cause in the induction phase of study C13007. The reasons for discontinuation in the maintenance arm appeared to be balanced between placebo, VDZ q4 and q8 weeks.

Table 11 Patient Disposition in 13007- Induction[5]

Patient Disposition – Induction Phase

	Induction Cohort 1 ITT Population[a]		Induction Cohort 2[b] Open-label	VDZ Combined	Total
	PLA N = 148	VDZ N = 220	VDZ N = 747	N = 967	N = 1115
Randomized/ assigned	148	220	748[c]	968	1116
Safety Population[d]	148 (100)	220 (100)	747 (100)	967 (100)	1115 (100)
ITT Population[e]	148 (100)	220 (100)		220 (23)	368 (33)
Per-Protocol Population[f]	141 (95)	205 (93)		205 (21)	346 (31)
Completed Induction Phase[g]	137 (93)	199 (90)	674 (90)	873 (90)	1010 (91)
Discontinued (reason)	11 (7)	21 (10)	73 (10)	94 (10)	105 (9)
Adverse event[h]	7 (5)	9 (4)	24 (3)	33 (3)	40 (4)
Protocol violation(s)	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Lack of efficacy	1 (< 1)	3 (1)	28 (4)	31 (3)	32 (3)
Study terminated by sponsor	0	0	0	0	0
Withdrawal of consent	3 (2)	9 (4)	15 (2)	24 (2)	27 (2)
Lost to follow-up	0	0	3 (< 1)	3 (< 1)	3 (< 1)
Other	0	0	2 (< 1)	2 (< 1)	2 (< 1)

Source: Table 14.1.1.2BP.

Abbreviations: ITT = Intent-to-Treat; PLA = placebo; VDZ = vedolizumab.

a All patients enrolled in Cohort 1 who were randomized to blinded induction treatment with vedolizumab or placebo.

b All patients enrolled in Cohort 2 who received open-label vedolizumab induction treatment.

c One patient enrolled in Cohort 2 withdrew from the study prior to dosing and is excluded from all analyses.

d Safety Population consists of all patients who received any amount of study drug during the Induction Phase based on what they actually received.

e ITT Population consists of all randomized patients who received any amount of blinded study drug during the Induction Phase based on what they were randomized to receive.

f Per-Protocol Population consists of all randomized patients who met prespecified criteria (Section 10.2.2-I).

g Defined as completed dosing at Weeks 0 and 2 and completed the predose assessments at Week 6.

h One additional ITT placebo patient is presented in Table 33 as discontinuing due to an AE; this patient is not counted here as the AE that led to discontinuation was not treatment emergent.

[5] Sponsor's Table 6 Clinical Study Report C13007 p. 116

Table 12 Disposition C13007 Maintenance (ITT population only)[6]

	Maintenance ITT (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)		
	PLA N = 153	**VDZ Q8W N = 154**	**VDZ Q4W N = 154**
Completed induction treatment	153 (100)	154 (100)	154 (100)
Randomized/assigned	153 (100)	154 (100)	154 (100)
Randomized but not dosed	0	0	0
Safety Population	153 (100)	154 (100)	154 (100)
ITT Population	153 (100)	154 (100)	154 (100)
Per-Protocol Population	147 (96)	149 (97)	144 (94)
Completed study	64 (42)	73 (47)	82 (53)
Discontinued (reason)	89 (58)	81 (53)	72 (47)
Adverse event	15 (10)	12 (8)	9 (6)
Protocol violation(s)	1 (< 1)	2 (1)	3 (2)
Lack of efficacy	64 (42)	58 (38)	48 (31)
Study terminated by sponsor	0	0	0
Withdrawal of consent	7 (5)	6 (4)	9 (6)
Lost to follow-up	1 (< 1)	3 (2)	2 (1)
Other	1 (< 1)	0	1 (< 1)
Enrolled into C13008	127 (83)	126 (82)	122 (79)

[6] Adapted from sponsor's table 44 Clinical Study Report C13007 p. 197

C13011

Table 13 Disposition in C13011 - Induction Only[7]

Patient Disposition

	TNFα Antagonist Failure ITT Subpopulation			Overall ITT Population		
	PLA N = 157	VDZ N = 158	Total N = 315	PLA N = 207	VDZ N = 209	Total N = 416
Randomized	157	158	315	207	209	416
Safety Population[a]	157 (100)	158 (100)	315 (100)	207 (100)	209 (100)	416 (100)
ITT Population[b]	157 (100)	158 (100)	315 (100)	207 (100)	209 (100)	416 (100)
Per-Protocol Population[c]	145 (92)	147 (93)	292 (93)	194 (94)	192 (92)	386 (93)
Completed study[d]	145 (92)	151 (96)	296 (94)	192 (93)	196 (94)	388 (93)
Enrolled into C13008	144 (99)	150 (99)	294 (99)	190 (99)	194 (99)	384 (99)
Discontinued (Reason)	12 (8)	7 (4)	19 (6)	15 (7)	13 (6)	28 (7)
Adverse event	6 (4)	2 (1)	8 (3)	8 (4)	4 (2)	12 (3)
Protocol violation(s)	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
Lack of efficacy	4 (3)	0	4 (1)	5 (2)	1 (< 1)	6 (1)
Withdrawal of consent	2 (1)	3 (2)	5 (2)	2 (< 1)	4 (2)	6 (1)
Lost to follow-up	0	1 (< 1)	1 (< 1)	0	3 (1)	3 (< 1)

Source: Table 14.1.1.2T, Table 14.1.1.2.

Abbreviations: ITT = Intent-to-Treat; PLA = placebo; TNFα = tumor necrosis factor alpha; VDZ = vedolizumab.

Percentages are based on number of patients in the Overall ITT Population, except for the percentage of patients enrolled into Study C13008, which uses the number of patients who completed study as the denominator.

a Safety Population consists of all patients who received any amount of blinded study drug based on what they actually received.

b ITT Population consists of all randomized patients who received any amount of blinded study drug based on what they were randomized to receive.

c Per-Protocol Population consists of all randomized patients who met prespecified criteria, as defined in Section 9.10.2.3.

d Completed study is defined as patients who completed the Week 10 assessments.

6.1.4 Analysis of Primary Endpoint(s)

Study C13007 was designed to demonstrate the efficacy of vedolizumab in patients with moderately to severely active CD, defined by CDAI of 220 to 450 points, and any of the following: serum C-reactive protein (CRP) concentration > 2.87 mg/L, colonoscopy demonstrating ≥ 3 non-anastomotic ulcers or ≥ 10 aphthous ulcers, or fecal calprotectin concentration > 250 mcg/g stool in conjunction with ulceration. The upper bound of

[7] Sponsor's Table 10-1 Clinical Study Report C13011

CDAI was modified from 480 to 450 when, approximately 6 months after study initiation, blinded review showed that the baseline disease activity scores from the first 50 patients were substantially higher than anticipated and not in alignment with the study objectives of including patients with moderately to severely active disease. The applicant states that the revised upper bound of 450 to define a study population with moderately to severely active disease is the same as that used in other registration studies for the approved TNFα antagonist therapies at the time of protocol development. Eligible patients had to have failed treatment with conventional therapy (i.e., corticosteroids and/or immunomodulators)[8] or TNFα antagonists. Immunomodulators were defined as 6-mercapotopurine (6-MP), azathioprine (AZA), and methotrexate (MTX). There was no limitation on the number of TNFα antagonists that a patient could have failed; at the time this study was conducted, patients could have failed up to 3 different TNFα antagonists, and failure was defined as inadequate response, loss of response, or intolerance. Compared to other studies evaluating TNFα antagonist therapies, Study C13007 was different in its inclusion of patients with CD who had not responded to TNFα antagonist treatment (primary nonresponders). Because the applicant intends vedolizumab for a broad population of patients, enrollment of patients who had failed TNFα antagonist therapies was limited to approximately 50% of the ITT Induction and Maintenance populations.

Disease activity was measured using the CDAI. The sponsor recognized that the disease activity for the first 50 enrolled patients was higher than expected and therefore modified the protocol (amendment 6 to study C13007) by adding the endpoint of enhanced clinical response (defined as a decrease from baseline in CDAI of at least 100 points) at Week 6 primary to the primary efficacy endpoint of clinical remission (defined as CDAI ≤ 150) at Week 6 [9].

Other than the Hochberg method used to control Type I error for the primary induction endpoints, the same statistical approach for controlling Type I error in Study C13006 was used in Study C13007.

Study C13011: Consistent with its objective, patients in Study C13011 were primarily patients with CD who had failed prior TNFα antagonist therapy, and 75% of the patients could have failed up to 3 different TNFα antagonist therapies, thereby selecting a patient population that is difficult to treat and has limited to no treatment options. To support the efficacy of vedolizumab in the broader patient population, the study also enrolled patients who had not yet received TNFα antagonist therapy, but had previously failed treatment with corticosteroids and/or immunomodulators[10]. Like Study C13007, Study C13011 included patients with CD who had not responded to TNFα antagonist treatment (primary non-responders). Patients had moderately to severely active CD,

[8] US trial participants had to have failed more than just corticosteroid treatment
[9] These were not co-primary endpoint in the sense of a logical AND but two equally ranked endpoint (logical OR).
[10] US patients had to have failed more than just corticosteroids

defined by baseline CDAI between 220 and 450, consistent with registration studies for new CD therapies.

The rationale for stratification of randomization to control for confounding factors in Study C13011 was similar to that used in the Induction Phase of Study C13007. Stratification factors included previous failure of TNFα antagonist therapy or no previous treatment with TNFα antagonist therapy, concomitant use of oral corticosteroids, and concomitant use of immunomodulators.

Disease activity was measured using CDAI and the primary endpoint was defined as clinical remission at Week 6 in TNFα antagonist-failure patients. Based on blinded results from Study C13007, the sponsor hypothesized that a third induction dose or longer duration of dosing could increase the rate of clinical remission measured at 10 weeks. Therefore, an additional dose and increased length of assessment were chosen for evaluation as part of the secondary endpoints in Study C13011, which allowed for evaluation of remission at the Week 10 time point. It also permitted the evaluation of sustained effects of induction therapy.

The primary endpoint was tested using the CMH chi-square test at a 5% significance level with adjustment for the stratification factors. To maintain the overall Type I error rate at 5%, the secondary endpoint analyses were performed sequentially and only if the comparison for the previous secondary endpoint was significant.

Crohn's Disease: Efficacy Results from Studies C13007 and C13011

Remission at Week 6 in the overall population was 1 of 2 primary endpoints in Study C13007 and the first ordered secondary endpoint in Study C13011. Data concerning the efficacy of 300 mg of vedolizumab for the induction and maintenance treatment of patients with moderately to severely active CD were provided in Study C13007, a Phase 3, multinational, randomized, double-blind, placebo-controlled trial. Data concerning the efficacy of 300 mg of vedolizumab to induce remission in patients who have failed TNFα antagonist therapy were provided by the Phase 3 study, C13011.

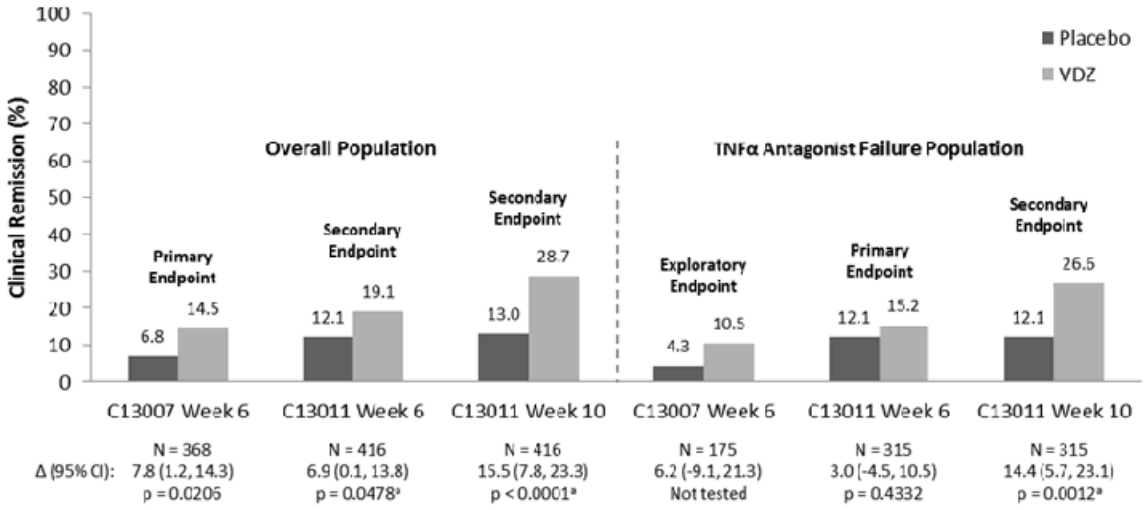
Study C13007 met the primary endpoint at Week 6 in the overall patient population. The prespecified Hochberg method was used to preserve alpha for the 2 primary endpoints; the p-value was < 0.025 on 1 of the 2 primary endpoints (clinical remission). For the second primary endpoint of enhanced clinical response (CDAI-100) at Week 6 in the overall population, the treatment difference favored vedolizumab but was not statistically significant. In the population of patients who had failed TNFα antagonist therapy in Study C13007, a greater proportion of vedolizumab-treated than placebo-treated patients were in remission at Week 6.

In Study C13011, clinical remission at Week 6 was numerically greater with vedolizumab than placebo in the primary analysis population of patients who failed TNFα antagonist therapy; however, the treatment difference compared to placebo was not statistically significant. Further hypothesis testing of secondary endpoints is

therefore exploratory. Remission rates were higher (with nominally significant p-values) compared with placebo at Week 10 following a third dose of vedolizumab in patients who failed TNFα antagonists. Similar results (with nominally significant p-values) were seen in the overall population in Study C13011, i.e., the treatment difference between vedolizumab and placebo was greater with vedolizumab at Week 6 and the difference increased at Week 10 following a third infusion. In Study C13011, continued remission for up to 4 weeks (i.e., remission at both Weeks 6 and 10) during induction was observed in greater proportions of vedolizumab-treated patients compared with placebo in both the overall (15.3% vs. 8.2%) and TNFα antagonist failure (12.0% vs. 8.3%) populations. Since the primary efficacy endpoint in Study C13011 did not reach statistical significance, analyses of all ordered secondary endpoints are considered exploratory.

Induction of remission and enhanced clinical response were both evaluated in Studies C13007 and C13011; the results from both studies are shown together in the following figures. The figures illustrate the remission and enhanced response rates for the overall population in each study, as well as the TNFα antagonist failure population, including both the Week 6 and Week 10 time points for Study C13011.

Figure 3 Clinical Remission at Week 6 in Study C13007 and at Weeks 6 and 10 in Study C13011 in the Overall and TNF Alpha Antagonist Failure Populations[11]



Patients who withdrew from study prematurely were classified as treatment failures. Δ (95%CI): adjusted percent vedolizumab - adjusted percent placebo and its 95% CI. a superscript for p-values: **P-values are descriptive**, based on the method controlling for Type I error.

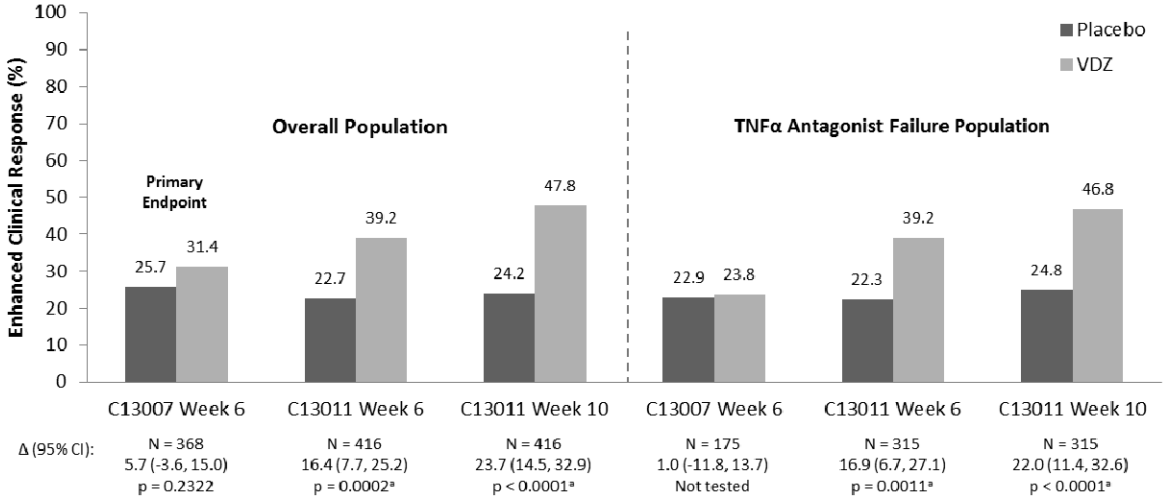
Left panel: clinical remission at week 6 was primary endpoint in C13007 and secondary endpoint in C13011, clinical remission at week 10 was secondary endpoint in C13011

Right panel: Clinical remission at Week 6 (TNF-alpha antagonist-failure population) was primary endpoint in 13011 and clinical remission at Week 10 (TNF-alpha antagonist- failure population and entire study population) was a secondary endpoint in C13011. Remission at week 6 in TNF-alpha-antagonist-failure population is an exploratory endpoint in C13007=

[11] Sponsor's Figure 4-9 Vedolizumab Clinical Overview p. 48

In both the overall and TNFα antagonist failure populations across both studies, rates of enhanced clinical response at Week 6 were numerically greater with vedolizumab than placebo. Enhanced clinical response at Week 6 was not statistically significant in Study C13007 where it was 1 of 2 primary endpoints. In Study C13011, enhanced clinical response at Week 10 was shown (exploratory analysis; nominally significant p value) in both the overall and TNFα antagonist failure populations. In Study C13011, although the clinical remission endpoint was not met at Week 6 in the TNFα antagonist failure population (primary analysis population), enhanced clinical response rates were higher than placebo at Week 6 (exploratory analysis; nominally significant p value).

Figure 4 Enhanced Clinical Response at Week 6 in Study C13007, Week 6 in Study C13011, and Week 10 in Study C13011 in the Overall and TNF Alpha Antagonist Failure Populations[12]



Source: Module 2.7.3-CD, Table 2-3 and Table 3-10; C13007 CSR, Table 14.3.1.8B; C13011 CSR, Table 14.3.1.7A, Table 14.3.1.8A, and Table 14.3.1.8AT.

Patients who withdrew from study prematurely were classified as treatment failures.

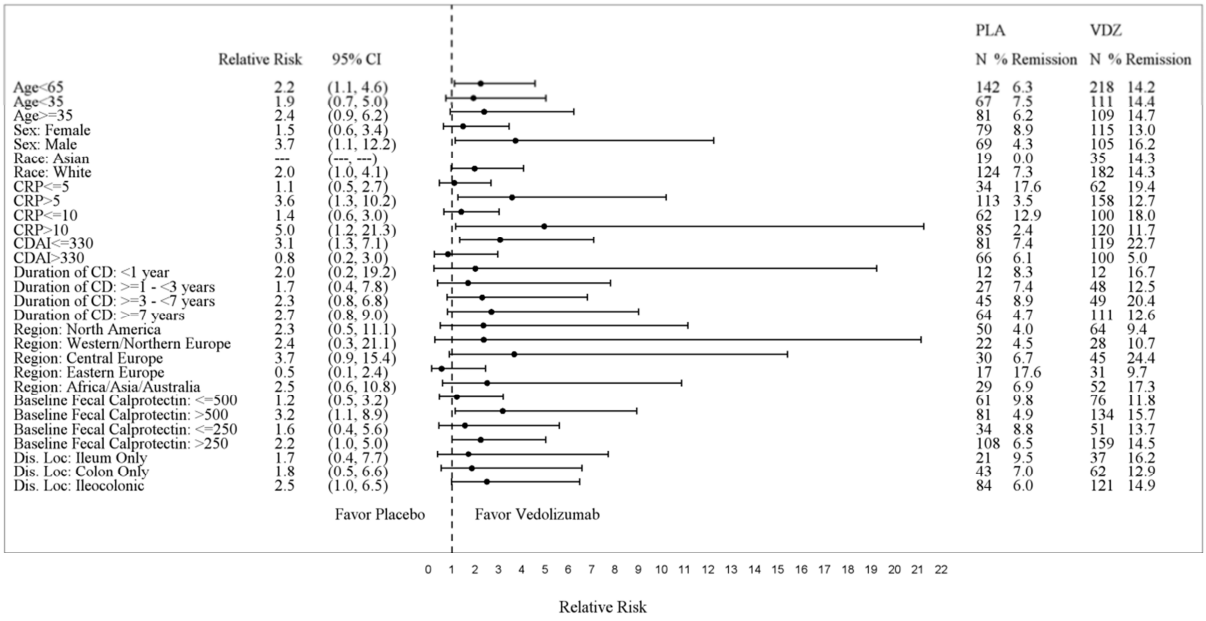
Δ (95%CI): adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

a P-values are descriptive, based on the method controlling for Type I error.

In Studies C13007 and C13011, the clinical remission rates with vedolizumab for induction therapy were generally consistent across underlying demographic factors and disease characteristics, such as age, gender, disease location, or baseline severity of disease (see following figures).

[12] Sponsor's Figure 4-10 Vedolizumab Clinical Overview p. 49

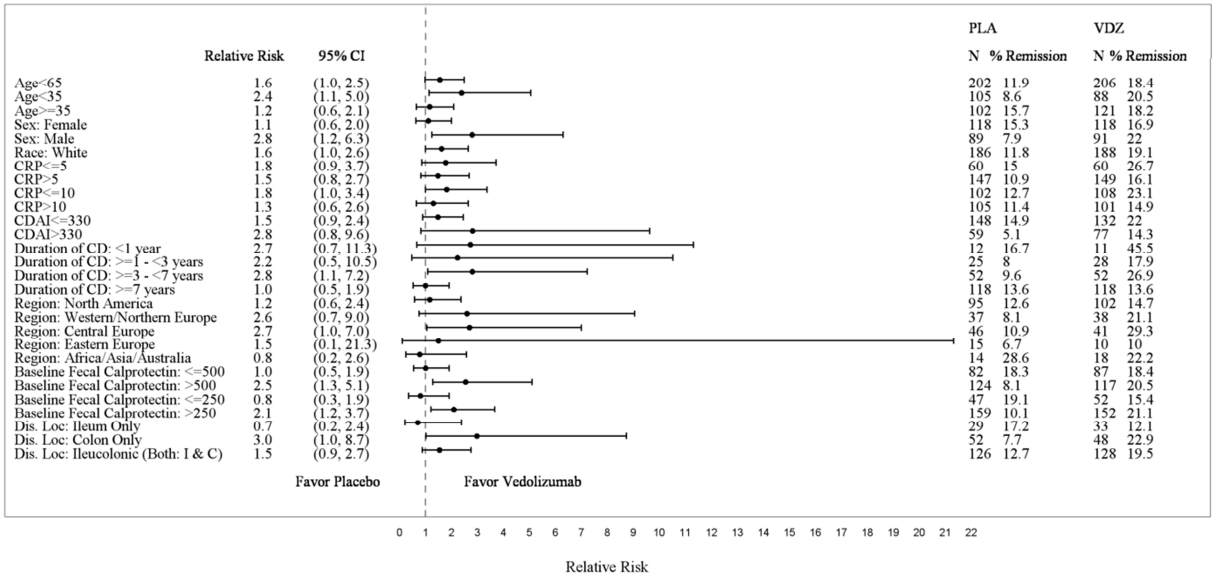
Figure 5 Relative Risk and 95% Confidence Interval for Subgroup Analyses of Clinical Remission at Week 6 – Induction Study ITT Population (Study C13007)[13]



If the number of patients was < 10, that subgroup was not presented. Relative risk > 1 favors vedolizumab.

Abbreviations: CD = Crohn's disease; CDAI = Crohn's disease activity index; CI = confidence interval; CRP = C-reactive protein; Dis. Loc = disease location; ITT = intent-to-treat; PLA = placebo; VDZ = vedolizumab.

Figure 6 Relative Risk and 95% Confidence Interval for Subgroup Analyses of Clinical Remission at Week 6 – Overall ITT Population (Study C13011)[14]



If the number of patients was < 10, that subgroup was not presented. Relative risk > 1 favors vedolizumab.

Abbreviations (see figure above).

[13] Sponsor's Figure 3.3 Summary of Clinical Efficacy for CD p. 127

[14] Sponsor's Figure 3.4 Summary of Clinical Efficacy for CD p. 128

In addition, the treatment benefit of vedolizumab for induction therapy was generally consistent in post hoc subgroup analyses in both Studies C13007 and C13011 conducted to evaluate the effect in patients with or without concomitant therapy with corticosteroids or immunomodulators.

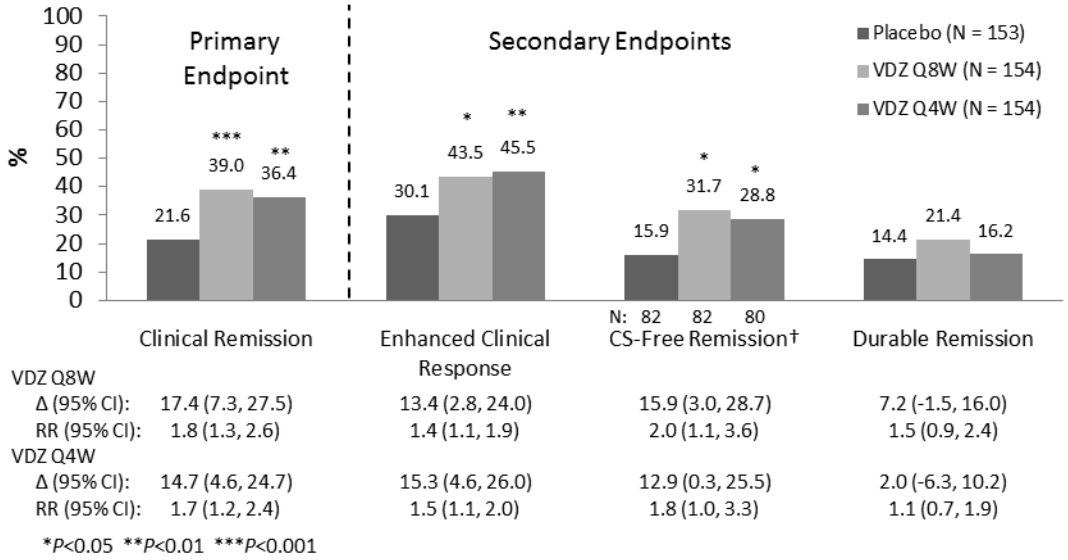
Patients who did not achieve clinical response at Week 6 continued to receive vedolizumab Q4W in Study C13007 after Week 6. In an exploratory analysis, the applicant showed that among patients who failed to demonstrate enhanced clinical response at Week 6, enhanced clinical response was observed at Weeks 10 and 14 for greater proportions of vedolizumab patients (16.0% and 21.7%, respectively) compared with placebo patients (7.2% and 11.6%, respectively). There was no clinically meaningful difference in clinical remission between treatment groups at these time points.

Crohn's Disease: Maintenance Study C13007

The efficacy of 300 mg of vedolizumab as maintenance treatment administered either Q4W or Q8W was evaluated in the maintenance arm of study C13007. As previously remarked, patients on vedolizumab who had shown a clinical response in the induction phase (decrease of CDAI by 70 points at week 6) had statistically higher rates of being in remission at week 52 than placebo patients. However, results for durable clinical remission were not significant for the q 8 week dosing interval. A claim for "maintenance" may therefore be problematic; this reviewer recommends that labeling avoid this term, instead describing the clinical trial findings (see Section 9.2).

The primary endpoint, a "snapshot" of clinical remission at Week 52, was statistically significant as were the first 2 of 3 ordered secondary endpoints (enhanced clinical response and corticosteroid-free clinical remission at Week 52), as presented in Figure 7.

Figure 7 Primary and Secondary Endpoints at Week 52 (Maintenance Study C13007)[15]



	Clinical Remission	Enhanced Clinical Response	CS-Free Remission†	Durable Remission
VDZ Q8W				
Δ (95% CI):	17.4 (7.3, 27.5)	13.4 (2.8, 24.0)	15.9 (3.0, 28.7)	7.2 (-1.5, 16.0)
RR (95% CI):	1.8 (1.3, 2.6)	1.4 (1.1, 1.9)	2.0 (1.1, 3.6)	1.5 (0.9, 2.4)
VDZ Q4W				
Δ (95% CI):	14.7 (4.6, 24.7)	15.3 (4.6, 26.0)	12.9 (0.3, 25.5)	2.0 (-6.3, 10.2)
RR (95% CI):	1.7 (1.2, 2.4)	1.5 (1.1, 2.0)	1.8 (1.0, 3.3)	1.1 (0.7, 1.9)

*P<0.05 **P<0.01 ***P<0.001

†CS tapering began in responders at 6 weeks; for others, as soon as a clinical response was achieved.

Source: Module 2.7.3-CD, Table 2-4.

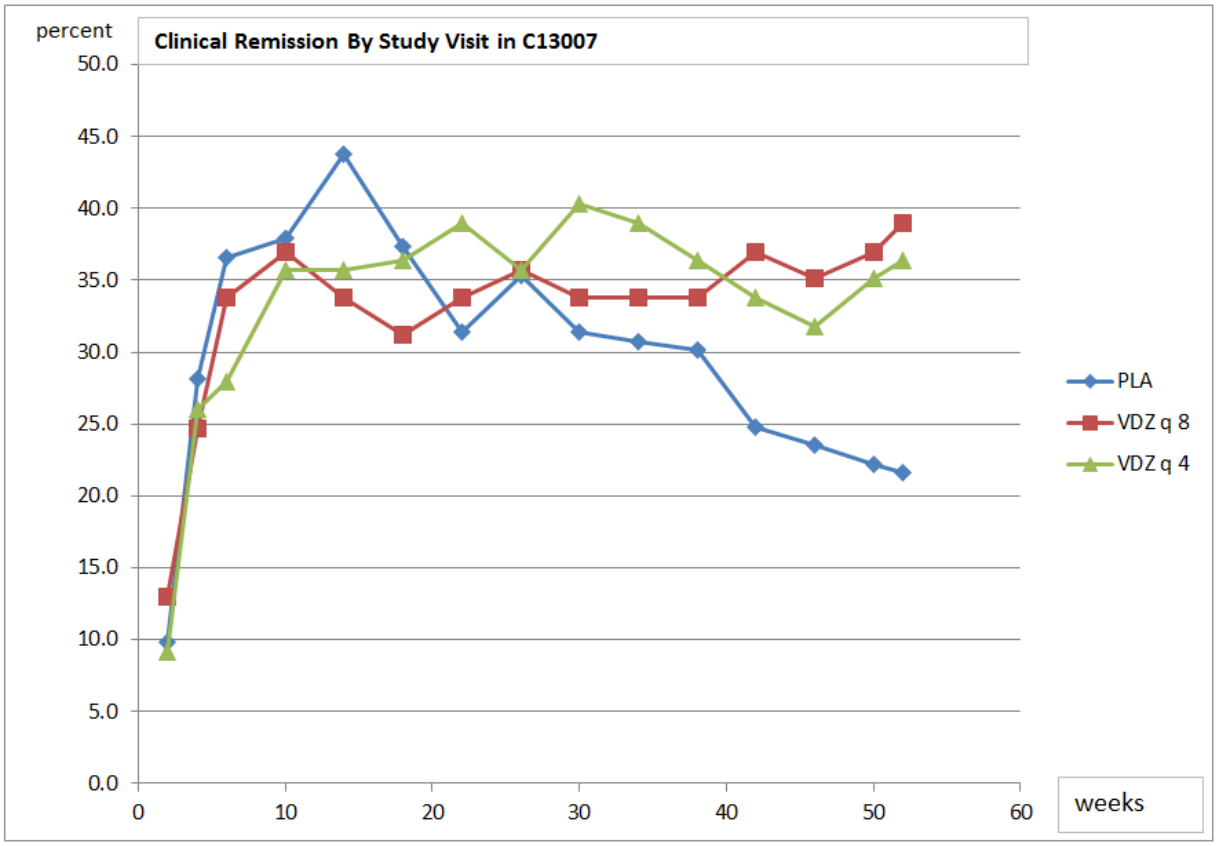
Patients who withdrew from study prematurely were classified as treatment failures.

Δ (95%CI): adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

[15] Sponsor's Figure 4-11 Vedolizumab Clinical Overview p. 50

The following table shows the proportion of patients enrolled in the maintenance phase of study C13007 that were in clinical remission at various points in time[16].

Figure 8 Clinical Remission By Study Visit Intent-to-Treat Population C13007



Source: Table 14.3.1.15CM Clinical Remission By Study Visit Intent-to-Treat Population p 502 Vedolizumab (MLN0002) Clinical Study Report C13007

[16] The patients were selected from those who had achieved clinical response at week 6 in the induction arm. This explains why at the beginning of the graph placebo and active are close together.

For ease of comparison the data are also presented in tabular form:

Table 14 Clinical Remission By Study Visit Intent-to-Treat Population C13007

Week	PLA	VDZ q 8	VDZ q 4
2	9.8	13	9.1
4	28.1	24.7	26
6	36.6	33.8	27.9
10	37.9	37	35.7
14	43.8	33.8	35.7
18	37.3	31.2	36.4
22	31.4	33.8	39
26	35.3	35.7	35.7
30	31.4	33.8	40.3
34	30.7	33.8	39
38	30.1	33.8	36.4
42	24.8	37	33.8
46	23.5	35.1	31.8
50	22.2	37	35.1
52	21.6	39	36.4

Source: Table 14.3.1.15CM Clinical Remission By Study Visit Intent-to-Treat Population p 502 Vedolizumab (MLN0002) Clinical Study Report C13007

It can be seen that the effect of active drug peaks at 10 weeks. It is however not clear whether this is a delayed effect of the induction dose given at week 2 or the effect of a third dose (first 'maintenance dose' at 6 weeks), or a combination.

Crohn's Disease: Discussion of Efficacy Results

The nature of the two endpoints in trial C13007 – Alternative primary endpoints, not co-primary endpoints

The sponsor's amendment 6 to study C13007 (introduction of a second primary endpoint) was motivated as follows:

> "The disease activity within the population of patients entering Study C13007 is substantially more active and more severe than was projected during the planning of this clinical study. These factors impact the overall C13007 study design as the hypotheses being tested are likely to be affected by this skewed population. In order to restore balance within the study and to ensure the generalizability of the study results to the overall Crohn's disease population, 2 key changes to the protocol will be implemented by this amendment:
>
> 1) Enhanced clinical response will be evaluated as a co-primary Induction Phase endpoint along with clinical remission (previously it represented the first key secondary endpoint).

2) CDAI range for eligibility will be limited to 220-450 points (previously 220-480 points)."

Further review of the amendment clearly reveals that the sponsor is using the term co-primary endpoint to mean that the two endpoints are "alternative endpoints". Authors of a consensus paper define the difference between alternative (logical OR) and co-primary (logical AND) as follows: "The word alternative is used to indicate that each primary endpoint is an alternative to other primary endpoints in determining the efficacy of the intervention. The multiple primary endpoints in the second case is called multiple co-primary endpoints to represent the simultaneous improvements required of the intervention."[17]

Results from study C13007 demonstrated the efficacy of vedolizumab to induce remission at Weeks 6 and also showed that at week 52, a single point in time, a higher proportion of patients on vedolizumab compared to placebo were in remission (statistically significant). Study C13007 met the primary endpoint at Week 6 in the overall patient population. There were 2 primary endpoints for the induction study of equal rank (not co-primary endpoint but alternative endpoints), induction of remission and enhanced clinical response. For the second primary endpoint of enhanced clinical response (CDAI-100) at Week 6 in the overall population, the treatment difference favored vedolizumab but was not statistically significant.

The efficacy of vedolizumab to induce remission at Weeks 6 and 10 is supported by the results from Study C13011. All patients in these studies were treatment experienced, i.e., had failed conventional therapy (corticosteroids and/or immunomodulators) and/or TNFα antagonist treatment including primary nonresponders. Patients who had failed at least 1 and up to 3 TNFα antagonists made up approximately 50% of patients in Study C13007 and 75% of patients in Study C13011; notably 27% and 49% of the patients in each study, respectively, had failed 2 or more TNFα antagonists, representing a patient population with few, remaining treatment options, such as natalizumab with its associated risk of progressive multifocal leukoencephalopathy (PML). In addition, in contrast to other studies evaluating TNFα antagonist therapies for patients with CD, the 2 pivotal studies evaluating vedolizumab were different in that they included primary treatment failures to TNFα antagonists, a population in need of new therapies with a different mechanism of action.

Possible reasons for meeting one but not two alternative endpoints in the Induction Phase of study C13007

As previously reviewed, one of two alternative primary endpoints, "induction of clinical remission" (CDAI ≤ 150), was met in C13007, but not "enhanced clinical response"

[17] Offen, Walter, Christy Chuang-Stein, Alex Dmitrienko, Gary Littman, Jeff Maca, Laura Meyerson, Robb Muirhead et al. "Multiple co-primary endpoints: medical and statistical solutions: a report from the multiple endpoints expert team of the Pharmaceutical Research and Manufacturers of America." *Drug Information Journal* 41, no. 1 (2007): 31-46.

(CDAI decrease of ≥ 100). The term “enhanced” was selected to call attention to the greater required decrease in CDAI; in previous registration trials, a decrease of the CDAI of ≥ 70 has been called “clinical response”. The second alternative primary endpoint (enhanced clinical response) was apparently added as alternative endpoint to the initially chosen “clinical response” to provide a safety net in case the patients that were initially enrolled (who were sicker than anticipated) would not be able to have a large enough drop in CDAI to be counted as remitters (even if they responded well to vedolizumab), hence, the use of the drop-by-100 endpoint (enhanced clinical response).

We now know that the outcome was the reverse of what was expected: The “induction of clinical remission” endpoint was met but the “enhanced clinical response” was not. This seems counterintuitive and requires further attempts at analysis. In many immune-mediated disease states, clinical trial endpoints are nested with the more stringent ones being subgroups of the less stringent one. Crohn’s Disease Activity Index (CDAI) 100 and remission are independently calculated from the raw CDAI score. While they are often concordant, the concordance is not 100%.

The following information request was issued to the applicant:

> “Perform an exploratory analysis of patient-level data to explain the divergent results between the two alternative primary endpoints in study 13007. Consider defining a “low-inflammatory subgroup” of patients (as evidenced by CRP and fecal calprotectin) and a “high-inflammatory” subgroup and analyze what proportion of patients in each subgroup contributed to the number of patients that achieved clinical remission or enhanced clinical response. Consider analyzing the relative contribution of the subscores of the CDAI to achieving the two alternative primary endpoints in the two subgroups, low-inflammatory and high-inflammatory in a multivariate analysis. When defining the cut points for the low- and high-inflammatory subgroups, use the cut-points you have chosen for your subgroup analysis (p.138 Clinical Study Report C13007 Figure 6).”

The CDAI is overwhelmingly being driven by “abdominal pain, diarrhea frequency, and general well-being”. In fact, the correlation between this 3-item short-CDAI to the 8-item full CDAI (as used in the vedolizumab studies), is excellent [Thia 2011]. However, these 3-items are also the paramount symptoms for diarrhea-predominant Irritable Bowel Syndrome (IBS-D). IBS is known to coexist with IBD in approximately 40% of cases [Halpin 2012]. More importantly, very high CDAI scores can easily be attained by patients who have IBS [Lahiff 2013]. With this background, this reviewer formulated the following hypothesis:

1. Patients whose predominant reason for high CDAI scores is underlying IBS are enriched in the *low*-inflammatory subgroup.
2. Patients whose predominant reason for high CDAI scores is inflammatory activity are enriched in the *high*-inflammatory subgroup.
3. Patients with predominantly IBS symptoms may have high CDAI levels that can exhibit significant decreases in response to the institution of new treatment (CDAI

decrease by 100), however, since anti-inflammatory agents do not address the underlying IBS pathomechanism, remission to a CDAI of less than 150 is less likely.

4. In consequence of the above, it is anticipated that the high inflammatory subgroup has relatively more remitters and the low-inflammatory subgroup relatively more "enhanced responders". However, since the low-inflammatory subgroup are enriched by placebo-responders, there should be little difference between active drug and placebo and a low "effect size".

Exploratory Analysis

As expected, the biomarker-defined high inflammatory group and low inflammatory group were equally distributed in patients with baseline CDAI scores ≤ 330 and > 330.

Table 15 Remission by Inflammatory Subgroup[18]

Table 39.31.4.1A
Clinical Remission at Week 6 - Evaluation in Subgroups Based on Inflammatory Status at Baseline
Intent-to-Treat Population

Clinical Remission [a]	PLA N=148	VDZ N=220
High Inflammatory	76	124
Number (%) Achieving Clinical Remission	3 (3.9)	18 (14.5)
95% CI	(0.8, 11.1)	(8.8, 22.0)
Difference from Placebo		10.6
95% CI for Difference from Placebo		(-3.7, 24.6)
Low Inflammatory	65	86
Number (%) Achieving Clinical Remission	7 (10.8)	12 (14.0)
95% CI	(3.2, 18.3)	(6.6, 21.3)
Difference from Placebo		3.2
95% CI for Difference from Placebo		(-7.3, 13.7)

High inflammatory subgroup is defined as "baseline CRP >2.87 and baseline fecal calprotectin >500" and low inflammatory subgroup is defined as otherwise. Patients with missing baseline CRP or missing baseline Fecal Calprotectin are excluded from this analysis.

[18] 1.11.3 Response to Agency Questions (Questions Received October 07, 2013) p. 62

Figure 9 Enhanced Clinical Response by Inflammatory Subgroup[19]

Table 39.31.4.1B
Enhanced Clinical Response at Week 6 - Evaluation in Subgroups Based on Inflammatory Status at Baseline
Intent-to-Treat Population

Enhanced Clinical Response [a]	PLA N=148	VDZ N=220
High Inflammatory	76	124
Number (%) Achieving Enhanced Clinical Response	19 (25.0)	37 (29.8)
95% CI	(15.3, 34.7)	(21.8, 37.9)
Difference from Placebo		4.8
95% CI for Difference from Placebo		(-7.8, 17.5)
Low Inflammatory	65	86
Number (%) Achieving Enhanced Clinical Response	16 (24.6)	30 (34.9)
95% CI	(14.1, 35.1)	(24.8, 45.0)
Difference from Placebo		10.3
95% CI for Difference from Placebo		(-4.3, 24.8)

High inflammatory subgroup is defined as "baseline CRP >2.87 and baseline fecal calprotectin >500" and low inflammatory subgroup is defined as otherwise. Patients with missing baseline CRP or missing baseline Fecal Calprotectin are excluded from this analysis.

The effect size for clinical remission at Week 6 is higher for the high inflammatory subgroup (10.6%) as compared to the low inflammatory subgroup (3.2%). This is expected based on the above hypotheses. However, as evident in the table above, the observed effect size for CDAI-100 response at Week 6 is higher for the low inflammatory subgroup (10.8%) which would contradict the hypothesis that CDAI-100 response is driven by patients with IBS who show a placebo effect.

The findings can be summarized as:

- Enhanced clinical response was more frequently observed in patients with low inflammatory activity, whereas clinical remission was more frequently seen in patients with high inflammatory activity.
- These findings could be considered hypothesis generating but are of scant relevance to the efficacy review of vedolizumab.

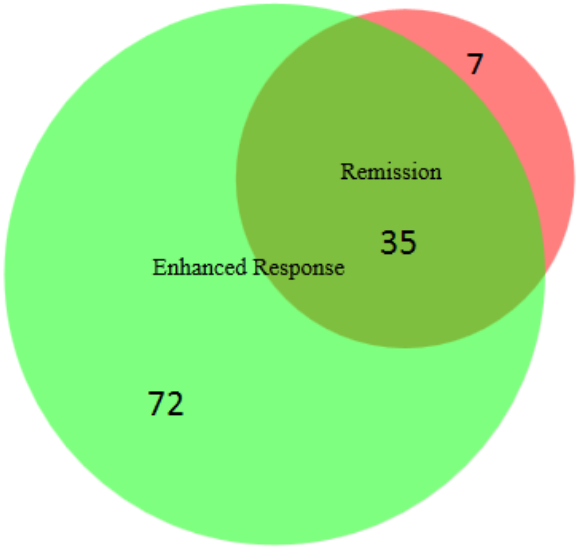
Unfortunately, the situation is further complicated by protocol violations as the following shows.

[19] Ibid. p.63

Relationship between the Two Alternative Endpoints "Clinical remission" and "Enhanced Clinical Response" in Study C13007 (Induction)

Clinical Remission was defined as a decrease of the baseline Crohn's Disease Activity Index (CDAI) to values ≤ 150. "Enhanced Clinical Response" was defined as a decrease of the CDAI by ≥ 100 points (CDAI-100 Response). "Enhanced Clinical Response" (CDAI-100 Response) is not a perfect subset of Clinical Remission since CDAI-100 Response is not necessarily a prerequisite for Clinical Remission. For example, a patient whose baseline score was 220 and whose reassessment score was 150 would meet the definition of clinical remission but not the definition of CDAI-100 Response. It is not necessarily easier to achieve CDAI-100 Response as opposed to Clinical Remission. However, in this trial, all 7 patients who met criteria for Clinical Remission but not "Enhanced Clinical Response" (CDAI-100 Response) (see Venn diagram below) had baseline CDAI scores that did not meet the eligibility criteria for the trial, i.e., their baseline scores were <220. Two of the seven were in the placebo arm (baseline scores 155 and 191). Five of the seven were in the vedolizumab arm (baseline scores 132, 142, 192, 213, and 218). In addition, two of these vedolizumab patients had baseline CDAI scores that met the protocol primary endpoint definition for remission (≤150).

Figure 10. Number of patients in C13007 in remission or "Enhanced Clinical Response" (CDAI-100 Response)



Overlap of **Clinical Remission** with "**Enhanced Clinical Response"** (at Week 6, VDZ and PBO: 7 patients in Clinical Remission did not meet criteria for "Enhanced Clinical Response"

Prepared from applicant's Table 39.31.4.3A 1.11.3 Response to Agency Questions (Questions Received October 07, 2013)

6.1.5 Analysis of Secondary and Exploratory Endpoints(s)

The secondary endpoint of reduction in CRP at Week 6 in Study C13007 was not achieved in the overall population.

Table 16 Changes from Baseline in CRP at Week 6 – Induction Study ITT-13007[20]

CRP Level (mg/L)	PLA N = 148	VDZ N = 220
Week 6[a]		
n	147	220
Baseline[b] mean (Std Dev)	23.6 (27.85)	24.1 (27.23)
Week 6 mean (Std Dev)	19.9 (30.05)	21.1 (26.92)
Change from baseline mean (Std Dev)	-3.6 (30.04)	-2.9 (16.28)
Change from baseline median	-0.5	-0.9
10th and 90th percentile	(-27.6, 12.1)	(-20.6, 10.3)
Wilcoxon[c] P-value		0.9288

Source: Table 14.3.1.6A.

CRP = C-reactive protein; ITT = intent-to-treat; PLA = placebo; Std Dev = standard deviation; VDZ = vedolizumab.

a If CRP was missing at Week 6, the last observation carried forward (LOCF) was used to carry out imputation.

b Baseline CRP was derived as the CRP value collected on Day 1 prior to dose; if missing, the screening CRP value was used.

c Wilcoxon Rank Sum test on the CRP change from baseline values (two-sided).

For Study C13011, DGIEP requested analyses for the TNFα antagonist-naïve population for the primary and secondary endpoints, which were already prespecified in the statistical analysis plan, and for the exploratory endpoints of enhanced clinical response at Week 10 and sustained enhanced clinical response. Despite the small numbers of patients who were naïve to TNFα antagonist therapy (50 placebo; 51 vedolizumab), treatment differences were observed favoring vedolizumab for all analyses (exploratory analyses; nominally significant p values) except for enhanced clinical response at Week 6, where a trend was observed with a 15% difference favoring vedolizumab treatment over placebo.

At the request of DGIEP, post hoc analyses of the primary and secondary efficacy endpoints at Week 52 of the Maintenance Study were performed by Induction Phase cohort (Cohort 1 [blinded] or Cohort 2 [open label]. Results for Cohort 2 were generally consistent with the results of the overall analyses (Cohorts 1 and 2 combined) and support the prespecified primary and secondary efficacy outcomes.

[20] Sponsor's Table 20 Clinical Study Report C13007 p. 139

Table 17 Clinical Remission at Week 52 (Protocol-Specified Definition) by Induction Phase Cohort – Maintenance Study ITT Population[21]

Clinical Remission,[a] n (%)	Cohort 1			Cohort 2		
	PLA N = 41	VDZ Q8W N = 40	VDZ Q4W N = 40	PLA N = 85	VDZ Q8W N = 82	VDZ Q4W N = 85
Number (%) achieving clinical remission	6 (14.6)	19 (47.5)	20 (50.0)	14 (16.5)	32 (39.0)	36 (42.4)
95% CI	(3.8, 25.5)	(32.0, 63.0)	(34.5, 65.5)	(8.6, 24.4)	(28.5, 49.6)	(31.8, 52.9)
Difference from placebo[b]		33.2	36.3		22.6	25.7
95% CI for difference from placebo		(13.1, 53.2)	(16.4, 56.2)		(9.2, 36.0)	(12.1, 39.3)
P-value for difference from placebo[c]		0.0012	0.0004		0.0009	0.0002
Relative risk[d]		3.3	3.5		2.4	2.6
95% CI for relative risk		(1.5, 7.4)	(1.6, 7.7)		(1.4, 4.1)	(1.5, 4.4)

Source: Table 14.3.1.32DM (post hoc).

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TNFα = tumor necrosis factor alpha; VDZ = vedolizumab.

a Clinical remission defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point at Week 52.

b Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

c P-values are based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no).

d Adjusted relative risk and its 95% CI.

[21] Sponsor's Table 3.1 Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA) p. 14

Table 18 Durable Clinical Response by Induction Phase Cohort – Maintenance Study ITT Population[22]

Durable Clinical Response,[a] n (%)	Cohort 1			Cohort 2		
	PLA N = 41	VDZ Q8W N = 40	VDZ Q4W N = 40	PLA N = 85	VDZ Q8W N = 82	VDZ Q4W N = 85
Number (%) achieving durable clinical response	7 (17.1)	25 (62.5)	23 (57.5)	23 (27.1)	44 (53.7)	42 (49.4)
95% CI	(5.6, 28.6)	(47.5, 77.5)	(42.2, 72.8)	(17.6, 36.5)	(42.9, 64.5)	(38.8, 60.0)
Difference from placebo[b]		45.3	41.2		26.7	22.5
95% CI for difference from placebo		(24.1, 66.6)	(20.5, 61.9)		(12.3,41.2)	(8.1, 36.8)
P-value for difference from placebo[c]		< 0.0001	< 0.0001		0.0003	0.0022
Relative risk[d]		3.7	3.4		2.0	1.8
95% CI for relative risk		(1.8, 7.5)	(1.7, 7.0)		(1.3, 2.9)	(1.2, 2.8)

Source: Table 14.3.1.32EM (post hoc).

Abbreviations and definitions: See table above.

Table 19 Mucosal Healing at Week 52 by Induction Phase Cohort – Maintenance Study ITT Population[23]

Mucosal Healing,[a] n (%)	Cohort 1			Cohort 2		
	PLA N = 41	VDZ Q8W N = 40	VDZ Q4W N = 40	PLA N = 85	VDZ Q8W N = 82	VDZ Q4W N = 85
Number (%) achieving mucosal healing	6 (14.6)	24 (60.0)	24 (60.0)	19 (22.4)	39 (47.6)	46 (54.1)
95% CI	(3.8, 25.5)	(44.8, 75.2)	(44.8, 75.2)	(13.5, 31.2)	(36.8, 58.4)	(43.5, 64.7)
Difference from placebo[b]		45.8	45.9		25.4	31.7
95% CI for difference from placebo		(24.8, 66.7)	(25.1, 66.7)		(11.2, 39.6)	(17.2, 46.3)
P-value for difference from placebo [c]		< 0.0001	< 0.0001		0.0005	< 0.0001
Relative risk[d]		4.1	4.2		2.1	2.4
95% CI for relative risk		(1.9, 9.1)	(1.9, 9.1)		(1.4, 3.4)	(1.6, 3.8)

Source: Table 14.3.1.32FM (post hoc).

Abbreviations and definitions: See table above.

[22] Sponsor's Table 3.2 Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA) p. 15
[23] Sponsor's Table 3.3 Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA) p. 16

Table 20 Durable Clinical Remission (Protocol-Specified Definition) by Induction Phase Cohort – Maintenance Study ITT Population[24]

Durable Clinical Remission,[a] n (%)	Cohort 1			Cohort 2		
	PLA N = 41	VDZ Q8W N = 40	VDZ Q4W N = 40	PLA N = 85	VDZ Q8W N = 82	VDZ Q4W N = 85
Number (%) achieving durable clinical remission	2 (4.9)	7 (17.5)	9 (22.5)	9 (10.6)	18 (22.0)	21 (24.7)
95% CI	(0.0, 11.5)	(5.7, 29.3)	(9.6, 35.4)	(4.0, 17.1)	(13.0, 30.9)	(15.5, 33.9)
Difference from placebo[b]		12.5	17.9		11.4	14.0
95% CI for difference from placebo		(-1.1, 26.1)	(3.1, 32.8)		(0.3, 22.6)	(2.7, 25.4)
P-value for difference from placebo[c]		0.0709	0.0176		0.0437	0.0155
Relative risk[d]		3.5	4.6		2.1	2.3
95% CI for relative risk		(0.8, 15.8)	(1.1, 19.7)		(1.0, 4.4)	(1.1, 4.8)

Source: Table 14.3.1.32GM (post hoc).

Abbreviations and definitions: See table above.

Table 21 Corticosteroid-Free Clinical Remission at Week 52 (Protocol-Specified Definition) by Induction Phase Cohort – Maintenance Study ITT Population[25]

Corticosteroid-Free Clinical Remission,[a] n (%)	Cohort 1			Cohort 2		
	PLA N = 25	VDZ Q8W N = 24	VDZ Q4W N = 24	PLA N = 47	VDZ Q8W N = 46	VDZ Q4W N = 49
Number (%) achieving corticosteroid-free clinical remission	4 (16.0)	9 (37.5)	12 (50.0)	6 (12.8)	13 (28.3)	21 (42.9)
95% CI	(1.6, 30.4)	(18.1, 56.9)	(30.0, 70.0)	(3.2, 22.3)	(15.2, 41.3)	(29.0, 56.7)
Difference from placebo[b]		21.5	34.0		15.5	30.1
95% CI for difference from placebo		(-3.3, 46.2)	(7.7, 60.3)		(-0.9, 31.9)	(12.1, 48.0)
P-value for difference from placebo[c]		0.0887	0.0112		0.0633	0.0010
Relative risk[d]		2.3	3.1		2.2	3.4
95% CI for relative risk		(0.8, 6.7)	(1.2, 8.4)		(0.9, 5.3)	(1.5, 7.5)

Source: Table 14.3.1.32HM (post hoc).

Trends favoring vedolizumab were observed for the primary endpoint and in all but 1 of the secondary endpoints (corticosteroid-free remission in Q8W group) in the Cohort 1 analyses.

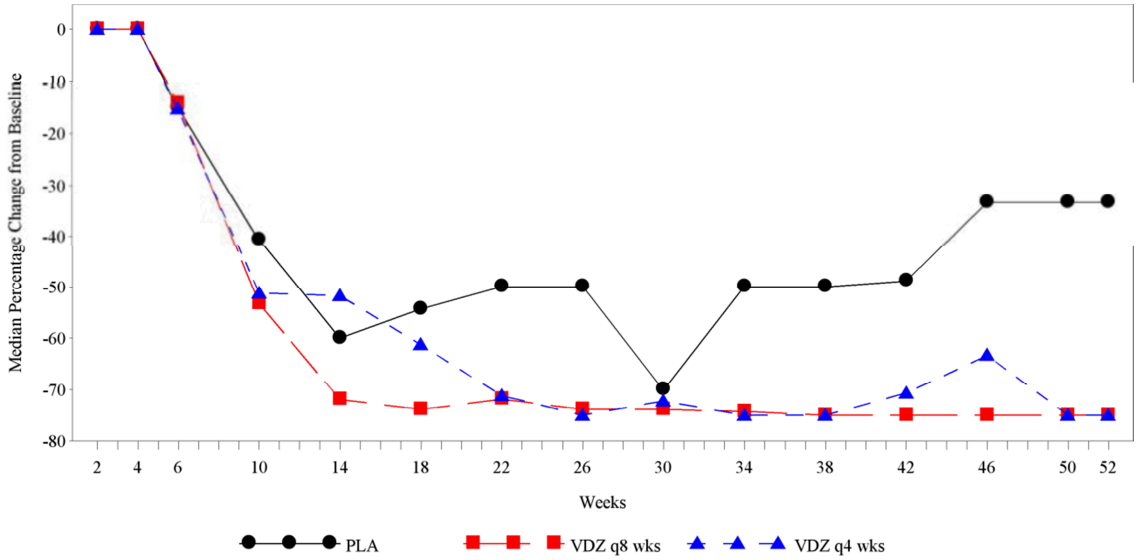
[24] Sponsor's Table 3.4 Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA) p. 18
[25] Sponsor's Table 3.5 Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA) p. 19

Trends favoring vedolizumab were observed for the primary endpoint and in all but 1 of the secondary endpoints (corticosteroid-free remission in Q8W group) in the Cohort 1 analyses.

In addition to corticosteroid-free remission, vedolizumab was also evaluated by whether patients who had discontinued corticosteroids for at least 90 and at least 180 days were in clinical remission at Week 52 (exploratory analyses). Of patients treated with corticosteroids at baseline, more patients treated with vedolizumab than placebo achieved corticosteroid-free clinical remission at Week 52 and had been corticosteroid free for 90 days, with treatment differences from placebo of 14.6% for Q8W (95% CI: 1.9, 27.3) and 9.1% for Q4W (95% CI: -3.1, 21.3). The corresponding treatment differences for vedolizumab patients who were corticosteroid-free for 180 days prior to Week 52 were 15.9% (95% CI: 3.2, 28.5) for Q8W and 9.1% (95% CI: -2.8, 21.1) for Q4W.

To further determine the potential benefit of vedolizumab in patients using corticosteroids, the sponsor conducted post hoc analyses of corticosteroid use by study visit (Figure 11). Because the data distribution curve for the doses of oral corticosteroids was highly skewed in Study C13007, post hoc analyses were performed on median change and median percent change from baseline in oral corticosteroid use. As shown in Figure 11, separation between the placebo and the vedolizumab groups started around Week 14, and clear separation was observed by Week 22, with maximal separation between groups occurring around Weeks 50 and 52. By Week 52, both vedolizumab treatment groups demonstrated a median 75% reduction from baseline (-10 mg/day) in oral corticosteroid use compared with the placebo group (33.3% reduction from baseline, -5.0 mg/day).

Figure 11 Post Hoc Analysis: Median Percentage Change From Baseline in Prednisone Equivalent Dose by Study Visit (Last Observation Carried Forward) (Study C13007)[26]

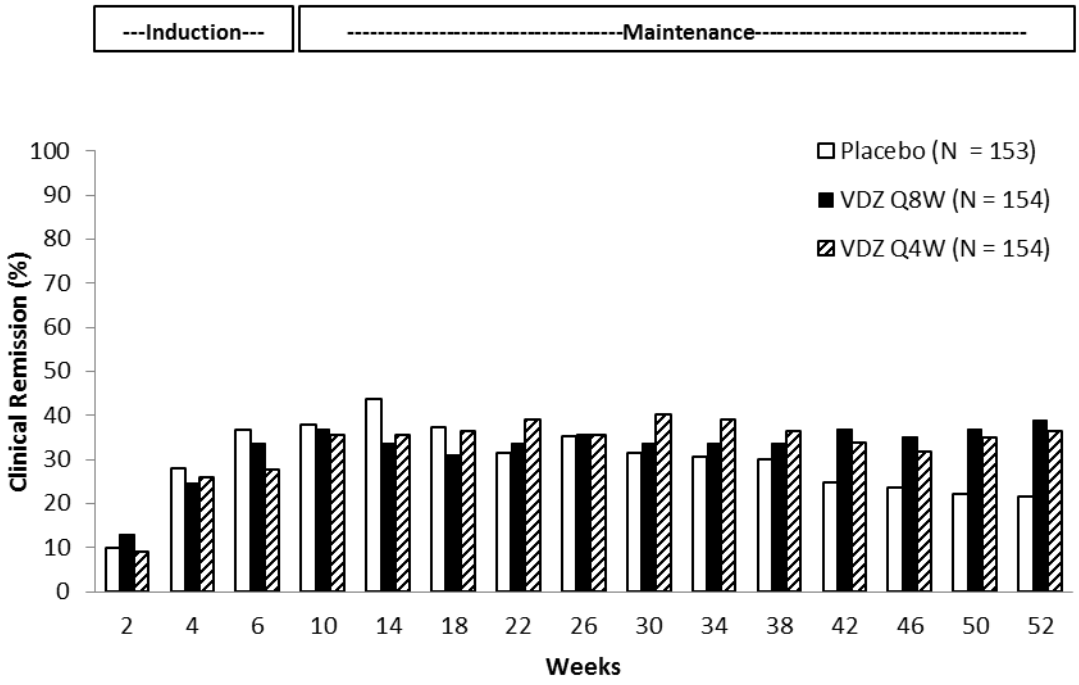


Source: Module 2.7.3-CD, Figure 2-3.

An analysis of clinical remission by study visit in patients who achieved clinical response at Week 6 of the C13007 Induction Study is shown in Figure 12. Patients in all 3 treatment groups received vedolizumab at baseline and at Week 2, and patients in all 3 treatment groups improved up to Week 10 (based on clinical remission). Among the patients who achieved response with vedolizumab induction treatment at Week 6 and were randomized, the percentages of vedolizumab-treated patients with clinical remission remained stable through Week 52 while the percentage of placebo-treated patients in clinical remission declined from Week 30 through Week 52.

[26] Sponsor's Figure 4-12 Vedolizumab Clinical Overview p. 52

Figure 12 Clinical Remission by Study Visit, Based on CDAI Score (Study C13007)[27]



Source: Module 2.7.3-CD, Figure 2-2.

Clinical remission is defined as a CDAI score of ≤ 150 points.

All patients received vedolizumab induction therapy and were re-randomized to maintenance therapy groups at Week 6.

Time to disease-worsening showed that, at Week 52, the risk of disease-worsening was higher for placebo-treated patients (24%) compared with the vedolizumab Q8W (19%) and Q4W (16%) groups. In addition, time to treatment failure showed that, at Week 52, the risk of treatment failure was higher for placebo-treated patients (43%) compared with the vedolizumab Q8W (39%) and Q4W (32%) groups.

6.1.6 Other Endpoints

The discussion of other endpoints is subsumed in the previous section.

6.1.7 Subpopulations

FDA issued the following information request:

"Studies C13006 and C13007: For each trial, provide subgroup analyses for the primary and secondary endpoints of both the Induction and Maintenance studies based on whether patients met the criteria outlined in Amendment 2 (28 Oct 2008) (US-specific amendment) to each protocol. Specifically, provide summary results for the primary and

[27] Sponsor's Figure 4-13 Vedolizumab Clinical Overview p. 53

secondary endpoints (for Induction and Maintenance) by treatment group for each of the two trials in the following two categories:

a) Met US protocol criteria (i.e., must have previously demonstrated an inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists [instead of the less stringent requirement of inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists or steroids] and must not have received concomitant immunomodulators beyond Week 6).

b) Did not meet US protocol criteria.
Note that if patients were enrolled outside the US but met the US protocol criteria described above, they should be included in category (a) above.

A similar request was issued for study C13011, however, overall, 96% of the patients enrolled met the US protocol criteria for Study C13011 and the results are therefore not informative.

In study C13007 54% of the patients enrolled met the US protocol criteria. For the primary endpoint clinical remission the results were as follows:

Table 22 Differences in Effect Size between US-protocol criteria met and not met

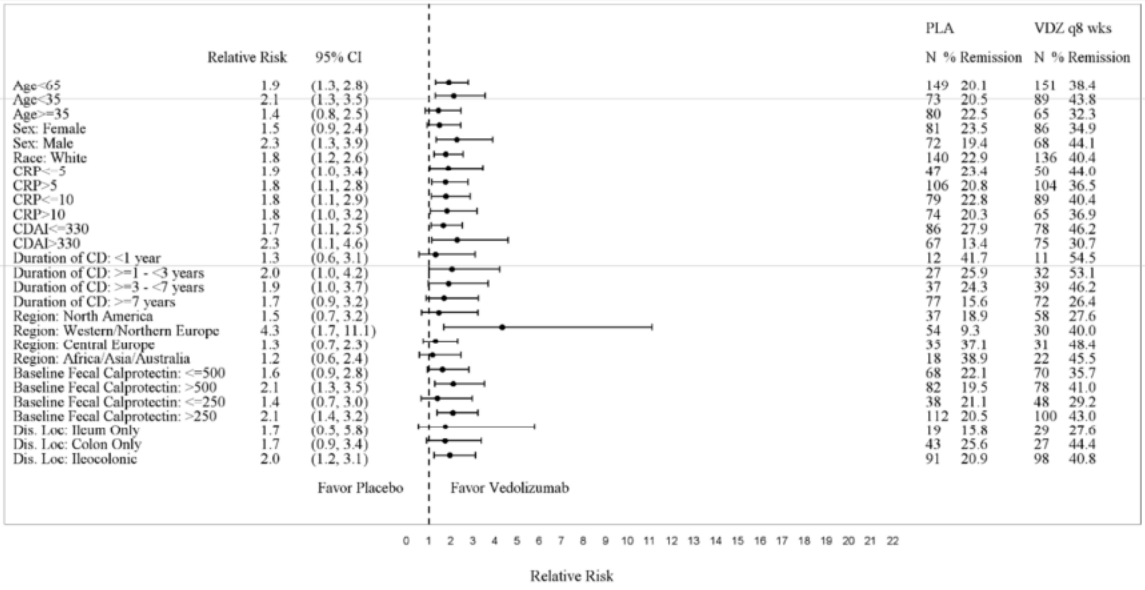
Primary Endpoint Effect size of VDZ (Difference from Placebo)	Induction (in remission at week 6)	Maintenance (in remission at week 52)	
		q 8 wks	q 4 wks
US-criteria met*	6.3 %	14.6 %	12.8 %
US-criteria not met#	9.8%	20.7 %	16.7 %

*US protocol criteria met: Induction: N=75 (PLA); N=120 (VDZ); Maintenance: N=78 (PLA); N=80 (VDZ Q 8 wks); N=78 (VDZ Q 4 wks)
#US protocol criteria not met: Induction: N=73 (PLA); N=100 (VDZ); Maintenance: N=75 (PLA); N=74 (VDZ Q 8 wks); N=76 (VDZ Q 4 wks)

As can be seen, effect sizes for the primary endpoint assessment seem to be numerically higher for the "US-criteria not met" subgroup. This appears plausible because meeting the US-criteria, especially needing to have failed more than just corticosteroids, is a higher hurdle for enrollment and may select for a more refractory population.

The results of other pertinent subgroup analyses were generally consistent among demographic and baseline disease characteristics in Study C13007 (see figure below).

Figure 13 Relative Risk and 95% Confidence Intervals for Subgroup Analyses of Clinical Remission at Week 52 for Vedolizumab Q8W vs Placebo – Maintenance Study ITT Population (Study C13007)[28]



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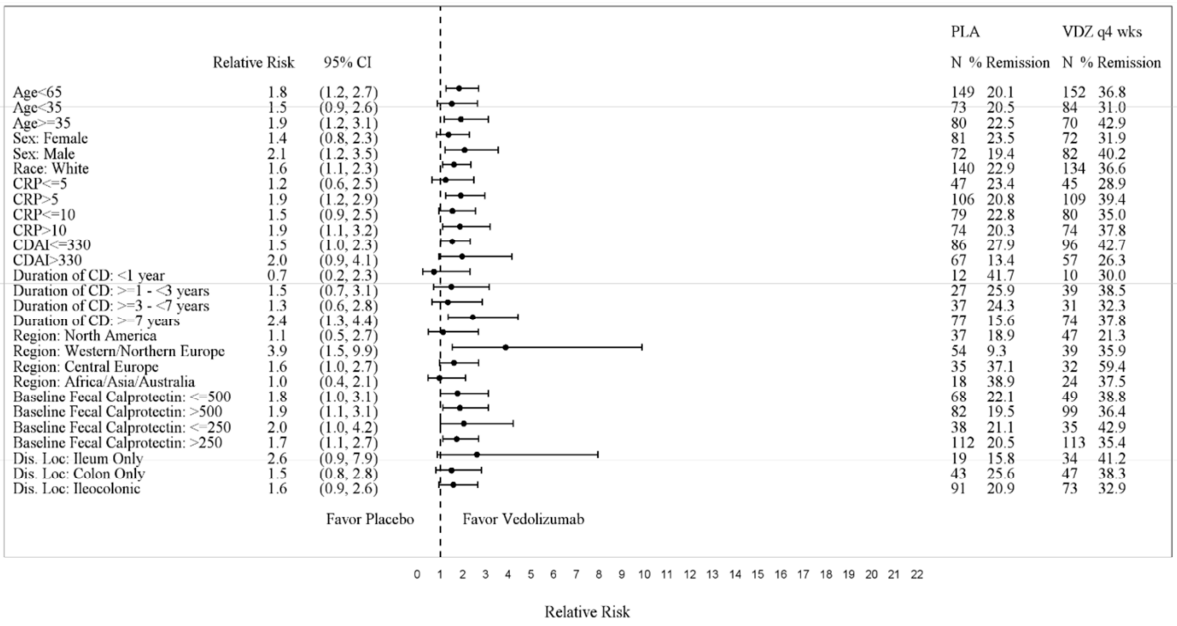
Only those subgroups with at least 10 patients in each treatment group are presented. Relative risk > 1 favors vedolizumab.
Abbreviations: CD = Crohn's disease; CDAI = Crohn's disease activity index; CI = confidence interval; Dis Loc = disease location; ITT = intent-to-treat; PLA =placebo; Q8W = dosing every 8 weeks; VDZ = vedolizumab.

[28] Sponsor's Figure 3-20 Summary of Clinical Efficacy CD p. 163

Figure 14 Relative Risk and 95% Confidence Intervals for Subgroup Analyses of Clinical Remission at Week 52 for Vedolizumab Q4W vs Placebo – Maintenance Study ITT Population (Study C13007)[29]

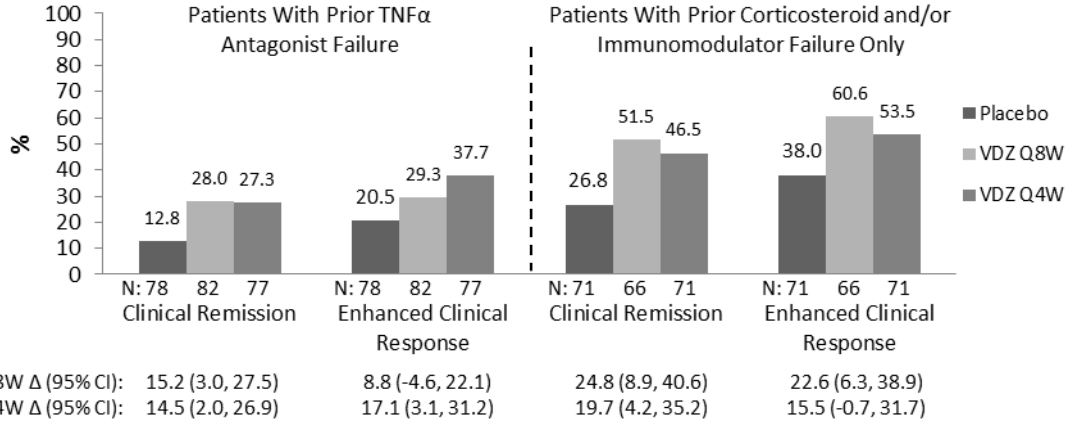


Only those subgroups with at least 10 patients in each treatment group are presented. Relative risk > 1 favors vedolizumab. Abbreviations see table above.

Analyses of Maintenance Study efficacy endpoints for patients who had previously failed TNFα antagonist therapy and for patients who had failed corticosteroids and/or immunomodulators but were naïve to TNFα antagonist therapy showed that, in patients who had failed conventional therapy (i.e., corticosteroids and/or immunomodulators) as well as in patients who had failed TNFα antagonists, a greater percentage of patients receiving 300 mg of vedolizumab Q8W or Q4W were in clinical remission or enhanced clinical response at Week 52 compared to placebo (Figure 15).

[29] Sponsor's Figure 3-21 Summary of Clinical Efficacy CD p. 164

Figure 15 Clinical Remission and Enhanced Clinical Response at Week 52 by Previous CD Therapy Failure (Maintenance Study C13007) Clinical Remission and Enhanced [30]



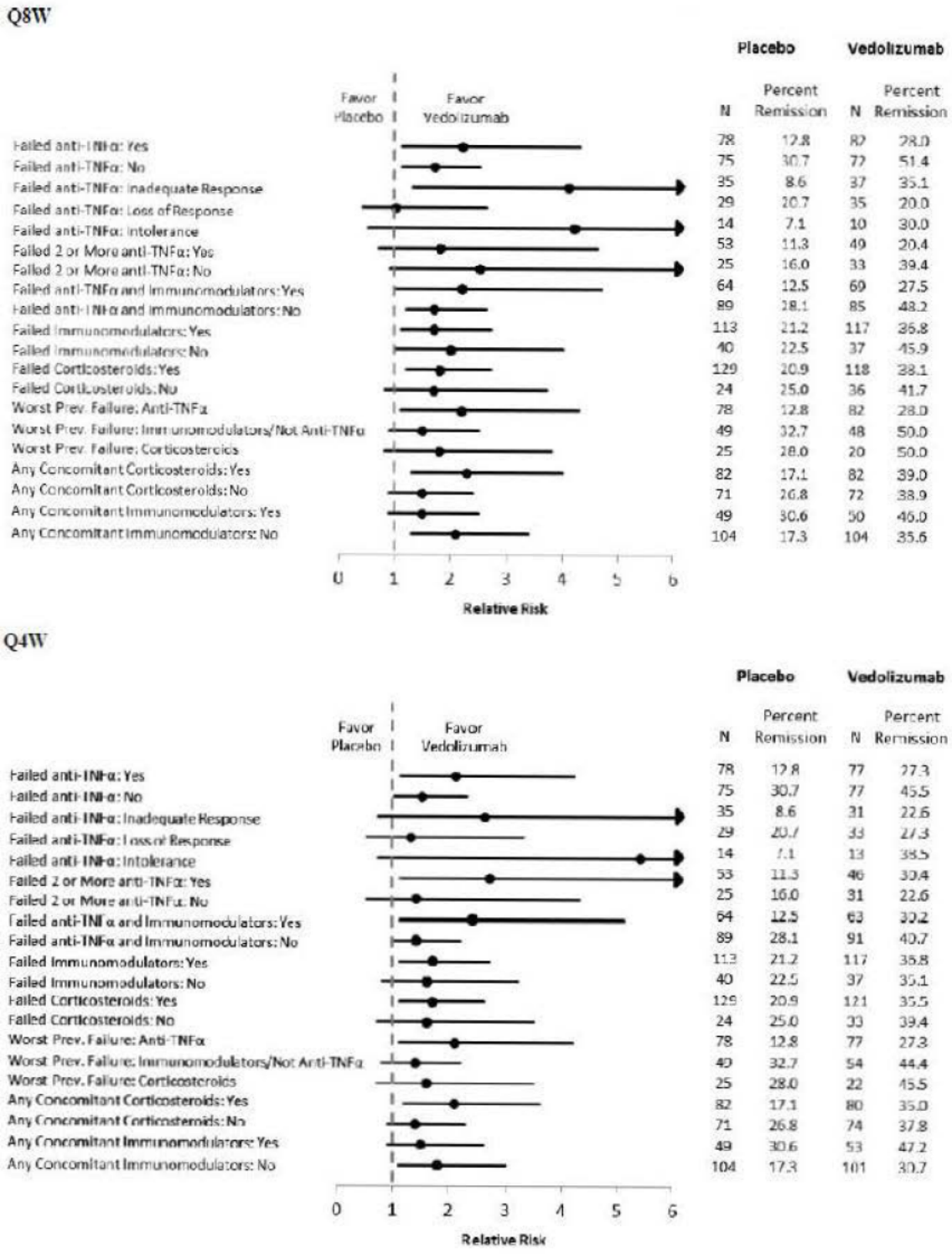
Source: Study C13007 CSR, Table 61.
Patients who withdrew from study prematurely were classified as treatment failures.

In analyses of clinical remission at Week 52 by prior failure type, all but one (loss of response) of the relative risk point estimates favored vedolizumab over placebo, including those patients who had failed TNFα antagonist therapy (e.g., post hoc analyses of patients with inadequate response and those who had failed at least 2 or more TNFα antagonists), immunomodulators, or corticosteroids (Figure 15).

In addition, the higher remission rate in vedolizumab than placebo for maintenance therapy was consistently observed in post hoc analyses conducted to evaluate the effect in patients with or without concomitant therapy with corticosteroids or immunomodulators (Figure 16).

[30] Sponsor's Figure 4-14 Vedolizumab Clinical Overview p. 54

Figure 16 Clinical Remission at Week 52 by Prior Treatment Failure and Concomitant Therapy (Maintenance Study C13007)[31]

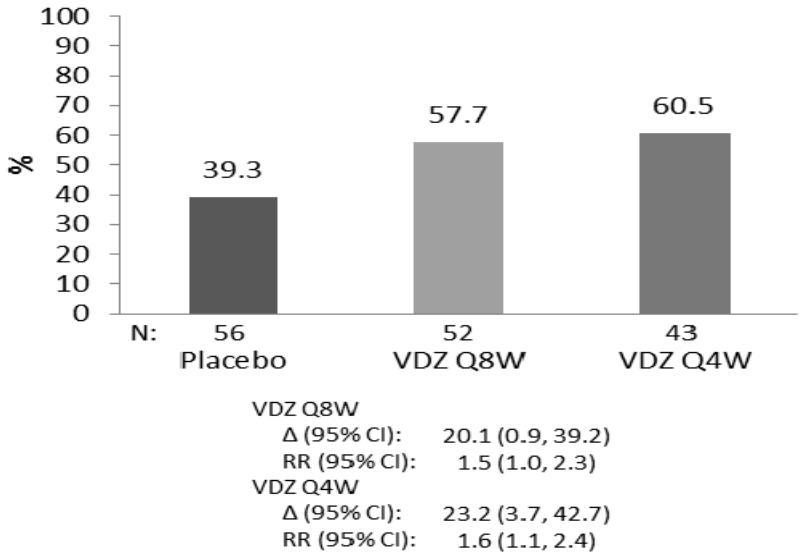


[31] Sponsor's Figure 4-15 Vedolizumab Clinical Overview p. 55

Greater proportions of patients in the vedolizumab groups achieved the ordered secondary endpoint of durable clinical remission (clinical remission in ≥ 80% of study visits) compared to placebo, although the difference from placebo was not statistically significant (Q8W 7.2% difference; Q4W 2.0% difference) (Figure 7). In addition, greater proportions of vedolizumab-treated patients in both treatment groups achieved durable clinical response at Week 52 (Q8W 10.8% difference, 95% CI: 0.3, 21.3; Q4W 11.3% difference, 95% CI: 0.8, 21.8) and durable enhanced clinical response at Week 52 (Q8W 11.5% difference, 95% CI: 1.7, 21.3; Q4W 9.4% difference, 95% CI: -0.4, 19.2), compared with placebo-treated patients.

In an additional post hoc analysis to assess the durability of remission with vedolizumab maintenance treatment, a greater proportion of vedolizumab-treated patients who had achieved clinical remission at Week 6 were also in remission at Week 52 compared to placebo-treated patients (Figure 17).

Figure 17 Post-Hoc Analysis: Clinical Remission at Week 52 for Patients Who Achieved Clinical Remission at Week 6 (Maintenance Study C13007)[32]



Source: C13007 EESA, Table 3-2 (post hoc)
Δ (95%CI): adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

[32] Sponsor's Figure 4-16 Clinical Overview p. 56

As rated by IBDQ, improvements in HRQOL at Week 52 were consistently greater for patients who received vedolizumab compared to patients who received placebo[33].

Table 23 Change From Baseline in IBDQ Total Score by Study Visit – Maintenance Study ITT Population (Study C13007)

IBDQ Total Score	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
Week 6			
N	152	153	154
Baseline mean (SE)	121.3 (2.54)	122.4 (2.38)	121.3 (2.56)
Week 52 mean (SE)	163.1 (2.46)	163.4 (2.28)	160.3 (2.79)
Mean change from baseline (SE)	41.9 (2.69)	41.1 (2.79)	38.9 (2.53)
Adjusted change from baseline[a]			
Mean (SE)	41.6 (2.28)	41.5 (2.28)	38.7 (2.27)
95% CI	(37.2, 46.1)	(37.0, 45.9)	(34.3, 43.2)
Difference in adjusted change from baseline vs.placebo[b]			
Mean (SE)		-0.2 (3.22)	-2.9 (3.22)
95% CI		(-6.5, 6.2)	(-9.2, 3.4)
Week 30			
N	121	120	126
Baseline mean (SE)	121.5 (2.87)	123.2 (2.85)	123.4 (2.85)
Week 52 mean (SE)	160.9 (3.17)	163.3 (3.35)	163.3 (2.92)
Mean change from baseline (SE)	39.4 (3.50)	40.0 (3.91)	39.9 (3.02)
Adjusted change from baseline[a]			
Mean (SE)	38.6 (2.99)	40.4 (3.00)	40.3 (2.93)
95% CI	(32.7, 44.5)	(34.5, 46.3)	(34.6, 46.1)
Difference in adjusted change from baseline vs.placebo[b]			
Mean (SE)		1.8 (4.23)	1.7 (4.18)
95% CI		(-6.6, 10.1)	(-6.5, 10.0)
Week 52			
N	82	79	92
Baseline mean (SE)	122.6 (3.42)	126.6 (3.52)	125.7 (3.27)
Week 52 mean (SE)	159.9 (3.95)	176.1 (4.05)	171.3 (3.61)
Mean change from baseline (SE)	37.3 (4.28)	49.5 (5.26)	45.6 (4.02)
Adjusted change from baseline[a]			
Mean (SE)	35.5 (3.81)	50.7 (3.88)	46.1 (3.60)
95% CI	(28.0, 43.0)	(43.0, 58.3)	(39.1, 53.2)

[33] SEALD generally does not recommend the use of IBDQ for (b) (4) purposes with the possible exception if the total score demonstrated a statistically and clinically significant improvement and each of the 4 domain scores showed an improvement.

Difference in adjusted change from baseline vs.placebo[b]		
Mean (SE)	15.1 (5.45)	10.6 (5.24)
95% CI	(4.4, 25.9)	(0.3, 21.0)

Source: Study C13007, Table 14.3.1.22AM.

Higher IBDQ scores indicate improvement in HRQOL.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; HRQOL = health-related quality

While these results met prespecified criteria for minimally important differences, it is doubtful that they are clinically meaningful (b) (4). Similar results were also observed for SF-36 and EQ-5D.

Few patients had a draining fistula at baseline (Day 0, placebo: 18; vedolizumab Q8W: 17; vedolizumab Q4W: 22). Although a small number of events were observed in this analysis, numerically greater proportions of patients in the vedolizumab Q8W (46.7%) and Q4W (23.8%) groups achieved fistula closure compared with the placebo group (11.1%).

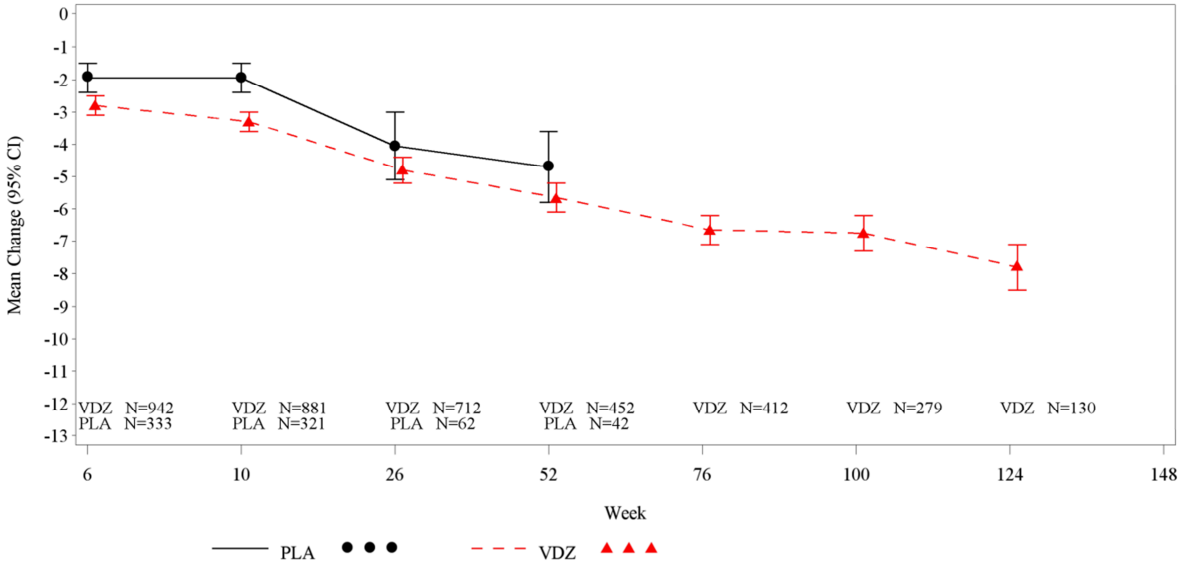
Too few patients (5 placebo, 3 vedolizumab Q8W, and 1 vedolizumab Q4W) required CD-related procedures or bowel surgeries in Study C13007 to draw any conclusions (3.3% placebo versus vedolizumab Q8W 1.9% and Q4W 0.6% for each endpoint). Among patients with elevated CRP (> 2.87 mg/L) levels at baseline, by Week 52, treatment differences from placebo in CRP levels, favoring vedolizumab, were noted for both the Q8W (median change: -5.5 mg/L; p = 0.0002) and Q4W (median change: -3.6 mg/L; p = 0.0170) groups. However, the overall values remained elevated.

Crohn's Disease: Results Beyond 52 Weeks

In Study C13008 a total of 1118 CD patients rolled over from previous qualifying vedolizumab studies. Of note, disease activity was assessed using only the Harvey Bradshaw Index (HBI) scores in Study C13008, while both CDAI and HBI were measured in the qualifying studies.

Long-term vedolizumab treatment beyond 52 weeks was assessed using integrated longitudinal data from Studies C13007 and C13011 with Study C13008. Consistent mean decreases in HBI scores and increases in clinical response and clinical remission rates were also observed from Week 6 in Study C13007 through 124 weeks of continuous vedolizumab exposure.

Figure 18 Mean Change in Baseline in HBI Score by Study Visit (Observed Case) – Persistent Efficacy Analysis Set



Source: Figure 18.1.1.6.

Abbreviations: CI = confidence interval; HBI = Harvey-Bradshaw index; PLA = placebo; VDZ = vedolizumab.

Persistent Efficacy Analysis Set includes C13007, C13011 and C13008 CD efficacy data. For C13007 patients who received vedolizumab during the C13007 Induction Study and were then randomized to placebo during the C13007 Maintenance Study, or for patients who were randomized to placebo in Induction Study C13007 or Study C13011, vedolizumab HBI efficacy data are only included from the time of enrollment in Study C13008. Data presented as of 16 July 2012.

Effect of Retreatment

Data on retreatment of patients following treatment interruption were obtained by evaluating patients who received 2 infusions of vedolizumab in the Induction Phase (Week 0 and Week 2), achieved a clinical response at Week 6, and were randomized to placebo in the Maintenance Study of C13007, followed by retreatment with vedolizumab Q4W in Study C13008. Of the 59 vedolizumab patients who terminated from Study C13007 during randomized placebo treatment, 45.8% were able to achieve remission with retreatment by Week 28 in the uncontrolled open label extension study 13008. The results also suggest that vedolizumab remains efficacious with retreatment following treatment interruptions of varying durations from 6 to 52 weeks with no apparent increase in AEs or infusion-related reactions during retreatment with vedolizumab.

Effect of Increased Dose Frequency

Both the Q8W and Q4W dosing regimens of vedolizumab showed statistically significantly higher remission rates compared to placebo in the treatment of CD. An analysis of 57 patients who transitioned from blinded vedolizumab Q8W in Study

C13007 to open-label vedolizumab Q4W in Study C13008 showed clinical remission rates of 22.8% (13 patients) at Week 28 and 31.6% (18 patients) at Week 52 compared to 3.5% (2 patients) at Week 0, indicating that at least some patients who did not benefit from the Q8W regimen appear to have derived benefit from more frequent dosing with the Q4W regimen. It needs to be noted that the open-label extension study 13008 was uncontrolled. No increase in AEs was noted between the 2 vedolizumab dosing regimens (Q8W and Q4W).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As previously discussed, based on blinded results from Study C13007, the sponsor hypothesized that a third induction dose or longer duration of dosing could increase the rate of clinical remission measured at 10 weeks. Therefore, an additional dose and increased length of assessment were chosen for evaluation as part of the secondary endpoints in Study C13011, which allowed for evaluation of remission at the Week 10 time point. It also permitted the evaluation of sustained effects of induction therapy.

Remission rates were higher (with nominally significant p-values) compared with placebo at Week 10 following a third dose of vedolizumab in patients who failed TNFα antagonists. Similar results were seen in the overall population in Study C13011, i.e., the treatment difference between vedolizumab and placebo was greater with vedolizumab at Week 6 and the difference increased at Week 10 following a third infusion.

The question whether a third dose during induction and a longer induction time interval increases the overall efficacy for vedolizumab may need further study as part of a PMC (see Section 1.4 of this Review). A more rigorous efficacy endpoint than CDAI such as a co-primary endpoint (logical AND) of SES-CD and CDAI, as recently used in other development programs, should be considered.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As is typical for monoclonal antibodies, vedolizumab has a long plasma-half life that varies according to dosing interval, dose, and patient factors, and is typically several weeks (see Clinical Pharmacology Review). Tolerance (in the sense of drugs with abuse potential) has not been described; however, loss of effectiveness occurs through neutralizing antibodies (see Clinical Pharmacology Review).

6.1.10 Additional Efficacy Issues/Analyses

Pending results of information request and statistics review.

7 Review of Safety

Safety Summary

Overall, the safety profile of vedolizumab was adequately characterized during the clinical development program. A total of 3326 subjects had received at least 1 dose of vedolizumab in

the clinical development program as of June 27, 2013. This included 1004 UC and CD patients who had received 24 or more infusions of vedolizumab with 4-weeks of follow-up.

The focus of the comparative safety review was on comparing adverse events across the induction and maintenance phase of the Phase 3 placebo-controlled trials which included a 52-week induction and maintenance trial (C13006 in ulcerative colitis and C13007 in Crohn's disease). The patients from Clinical Trials C13006 and C13007 are believed to be sufficiently similar that pooling of the data is appropriate and will increase the power to find any safety signals. In addition, these patients were exposed to vedolizumab at the proposed dose for licensure (300 mg) and are similar to patients who may receive this product in clinical practice. The focus of these comparisons is on the 1434 patients who received vedolizumab only throughout the trial (VDZ/VDZ) and the 297 patients who received only placebo (PLA/PLA). An additional 279 patients received vedolizumab during induction and were randomized to receive placebo during the maintenance phase (VDZ/PLA).

Serious adverse events were reported in 19% of patients receiving vedolizumab throughout, compared to 13% of patients who received placebo only. Serious infection adverse events and those considered drug-related occurred with similar frequency between the vedolizumab and placebo groups (serious infection AE 4% and 3% respectively, and drug-related SAE 3% and 2%, respectively). The most frequently reported serious AEs (≥ 1% of the VDZ/VDZ population) were related to underlying IBD and included Crohn's disease, ulcerative colitis, and anal abscess. The higher proportion of patients reporting at least 1 SAE in the vedolizumab group was largely driven by SAE reporting in C13007. There was a higher overall rate of serious adverse events in Trial C13007 for Crohn's disease, with 199 (24%) of patients in the combined vedolizumab group reporting at least 1 SAE, compared to 23 (16%) in the non-ITT placebo group.

Adverse events leading to clinical trial discontinuation was similar between the placebo groups and combined vedolizumab groups. The most common AEs resulting in study discontinuation from the combined vedolizumab group were ulcerative colitis and Crohn's disease.

One death (0.3%) occurred during the controlled clinical trial period in a patient receiving placebo, compared with 5 deaths 0.3%) in patients receiving vedolizumab. An additional 7 patients died in the open-label extension trial C13008, 3 with UC and 4 with CD. The events leading to death among the UC patients were respiratory failure, cerebrovascular accident, and pulmonary embolism. None of these events were determined to be related to study drug. Among the CD patients, traumatic intracranial hemorrhage, hepatic neoplasm, suicide, and sepsis led to patient deaths. Again, none of these deaths were determined to be related to the study drug, as per the clinical reviewer assessment.

The proportion of patients with at least 1 adverse event in studies C13006 and C13007 was 84%, 78% and 84% in the VDZ/VDZ, PLA/PLA, and VDZ/PLA group, respectively. The most commonly reported adverse events which occurred more commonly in the vedolizumab treated patients were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, and cough. All of these adverse events occurred in at least 5% of the combined vedolizumab group. The rates of common adverse events, when considered by patient-years, were similar between the combined vedolizumab group and the non-ITT placebo group. The frequency of nonserious AEs, categorized as "severe" was also similar between the 3 treatment groups in Studies C13006 and C13007. Thirteen percent of patients receiving VDZ/PLA reported severe AEs, compared to 14% receiving PLA/PLA and 15% in VDZ/VDZ. Crohn's disease, abdominal pain, and ulcerative colitis were the only AEs categorized as severe

which were reported in at least 1% of the combined vedolizumab group, and these occurred at similar frequencies in the 3 treatment groups.

A higher proportion of patients in vedolizumab treated groups reported 1 or more infectious AE, than in the placebo groups. In both the UC and CD populations, infections involving the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection) were the most commonly reported infection and occurred with greater frequency in vedolizumab treated patients than placebo. There was no increase in serious infection related AEs seen. Oronasal-associated lymphocytes show primary α4β7 expression, suggesting the MAdCAM-1 interactions have a role in nasal infections. The greater frequency of upper respiratory tract infections is consistent with vedolizumab's mechanism of action in inhibiting the α4β7-MAdCAM-1 interaction. There is the potential that this represents an off target event, however, and this should continue to be monitored in the post-marketing setting. Furthermore, labeling language indicating that vedolizumab is (b) (4) may be misleading.

Serious infections were reported in both controlled and open-label trials. Serious infections were more common in CD patients. In Study C13007, serious infections were reported in (5 (3%), 4 (3%), and 45 (6%) of patients in the VDZ/PLA, PLA/PLA, and VDZ/VDZ groups, respectively. Serious infections were reported by 20 patients in C13006 and at a similar frequency between dose groups (3% VDZ/PLA; 3% PLA/PLA; 2% VDZ/VDZ). Anal abscesses were the most frequently reported serious AE among CD patients, and the frequency was highest in the non-ITT vedolizumab group. Other serious adverse events reported included sepsis, tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegalovirus colitis.

No apparent signals for increased risk for an adverse event or any type of adverse event when assessing AEs by a variety of demographic factors was seen, including age, sex, geographic region, and prior IBD treatments. Patients with previous TNFα use had a higher overall rate of AEs, however, the AE rates were similar between treatment groups in this subset.

Since 2007, the vedolizumab clinical development program included a Risk Assessment and Minimization for PML (RAMP) program. The RAMP program was thorough, and no cases of PML were identified through the 120 day safety data cutoff. This included 1004 patients exposed to 24 or more vedolizumab infusions with 4-weeks of follow up and approximately 80% of whom received prior immunosuppressant therapy. Less than 1% of patients tested positive for JC viremia; JCV antibody testing was not included in the RAMP program. There were 0 cases of PML identified during the vedolizumab clinical development program to date.

7.1 Methods

A total of 3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as ofJune 27, 2013. This included 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. The safety populations for comparative safety analyses are defined in Table 24.

Table 24: Safety Populations and Definitions

Safety Population	Definition
PLA/PLA	patients who received continuous double-blind placebo throughout the entire 52-week trial (C13006 and C13007)

VDZ/VDZ	patients who responded to vedolizumab 300mg treatment during induction and were randomized to Q8W or Q4W vedolizumab 300mg (ITT vedolizumab), as well as those patients who did not respond to vedolizumab during the induction phase and received open label vedolizumab 300mg Q4W (non-ITT vedolizumab) during the maintenance phase (C13006 and C13007)
ITT vedolizumab	*patients who responded to vedolizumab 300mg treatment during induction and were randomized to Q8W or Q4W vedolizumab 300mg*
Non-ITT vedolizumab	*patients who did not respond to vedolizumab during the induction phase and received open label vedolizumab 300mg Q4W during the maintenance phase*
VDZ/PLA	patients who received vedolizumab during induction and were randomized to receive placebo during the maintenance phase. The clinical meaningfulness of this group is complicated by their vedolizumab exposure during induction (half-life of ~25 days), so this group will be presented separately from the non-ITT placebo group. The ITT-placebo group will also be included in the overall vedolizumab exposure groups. (C13006 and C13007)

CD Comparative Safety

To provide a comparative safety analysis in patients with CD, safety data from Clinical Trial C13007 will be presented and separated by treatment arms. The Maintenance Phase Safety Population includes safety data from all 1115 patients enrolled in C13007 from Week 0 through clinical trial completion, including patients who discontinued prior to the Maintenance Phase of the trial. The maintenance ITT populations will be compared and includes patients who responded to vedolizumab during induction and were randomized to either vedolizumab every 4 weeks, vedolizumab every 8 weeks, or placebo for the Maintenance Phase. To augment these comparisons, the non-ITT placebo group and the combined vedolizumab group will also be compared.

UC and CD Comparative Safety

The focus of the UC and CD comparative safety evaluation is on comparing adverse events from the phase 3 placebo-controlled trials which included a 52-week induction and maintenance trial (C13006 and C13007). Clinical Trial C13011 was an induction trial only and will not be included unless specified. This safety population includes safety data from all patients enrolled in these trials from Week 0 through trial completion. The patients from Clinical Trials C13006 and C13007 are believed to be sufficiently similar that pooling of the data is appropriate and will increase the power to find any safety signals. In addition, these patients were exposed to vedolizumab at the proposed dose for licensure of 300 mg and are similar to patients who may receive this product in clinical practice. The focus of these comparisons is on the 1434 patients in the combined vedolizumab group and the 297 patients in the non-ITT placebo group. The non-ITT placebo and combined vedolizumab groups are particularly relevant, as these patients stayed in the same treatment group throughout the 52 weeks, although some in the combined vedolizumab group received vedolizumab open label. An additional 279 patients received vedolizumab during induction and were randomized to receive placebo during the maintenance phase (ITT-placebo group).

Long-term Safety

The long-term UC and CD safety population focuses on safety data from Trial C13008, a long term extension study evaluating safety with continued vedolizumab in patients with UC or CD. This long-term safety population (N= 2243) includes both rollover patients (N=1822) and de novo patients (N=421). For patients who received vedolizumab in qualifying clinical trials and rolled into C13008, the frequency of AEs was analyzed across the originating trial and Trial C13008. For patients who received placebo during the previous trial, AEs were not counted during the time of placebo administration. For these patients and de novo patients, all AEs were summarized from the first dose of vedolizumab.

Exposure data and presentation of deaths and other specifically relevant AEs (i.e., PML) will use the entire safety population, controlled and uncontrolled studies in patients and healthy volunteers.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed primarily from Clinical Trials C13006 and C13007, and additional safety data was obtained from the ongoing open-label extension trial, C13008. See section 7.1 for additional details.

Table 25: Clinical Trials Used for Primary Safety Evaluation

Clinical Trial ID	Trial Design/No. of Centers	Trial Population	Treatment Arms	Number of patients by treatment entered/completed	Safety Endpoints
C13006	Phase 3, randomized, placebo-controlled, double-blind, multicenter trial/211	Male or female patients, aged 18 – 80, with moderately to severely active Ulcerative Colitis	VDZ 300 mg or placebo at Weeks 0 and 2	VDZ: 746/703 Placebo: 149/135	AEs, PML symptom checklist, plasma JC virus testing, vital signs, stool samples, ECG results, laboratory results (including standard hematology, clinical chemistry, coagulation, and urinalysis) Immunogenicity: blood samples for HAHA assessment
			VDZ 300 mg Q4W or Q8W or placebo from week 6 until week 52	ITT VDZ Q4W: 125/84 Non-ITT VDZ Q4W: 373/135 VDZ Q8W: 122/77 ITT Placebo: 126/48 Non-ITT Placebo: 149/30	
C13007	Phase 3, randomized, placebo-controlled, double-blind, multicenter trial/285	Male or female patients, aged 18 – 80, with moderately to severely active Crohn's Disease	VDZ 300 mg or placebo at Weeks 0 and 2	VDZ: 968[a]/873 Placebo: 148/137	
			VDZ 300 mg Q4W or Q8W or placebo from week 6 until week 52	ITT VDZ Q4W: 154/82 Non-ITT VDZ Q4W: 506/163 VDZ Q8W: 154/73 ITT Placebo: 153/64 Non-ITT Placebo: 148/42	
C13008	Phase 3, open-label, long-term, safety extension trial/292	Male or female, aged 18 – 80, rolling over from previous qualifying VDZ studies. De novo patients were also enrolled but only included in safety analyses.	VDZ 300 mg Q4W	Total: 2243/1411	

[a] 1 patient withdrew before receiving a single dose

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) was used for coding all AEs. Specifically, AEs were coded and grouped into Preferred Term (PT), High Level Term (HLT), and System Organ Class (SOC), using MedDRA Version 14.0. Based on a FDA Investigators Rapid Review System (FIRRS) MedDRA term matching comparison looking at a random sample of 20% of AE terms and this reviewer's review of all AE coding (verbatim terms to dictionary terms), the AE data is adequately coded.

An adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not it was considered to be study drug related. This included any increase in severity or frequency of a preexisting condition. Signs and symptoms of IBD were only to be collected if they developed or worsened during the clinical trial. All AEs were categorized according to severity:

- mild: awareness of event but easily tolerated
- moderate: discomfort enough to cause some interference with usual activity
- severe: inability to carry out usual activity

In addition, the following causal relationship categories were used for all vedolizumab clinical trial AEs:

- related: there was a reasonable causal relationship between the study drug and the AE.
- unrelated: there was not a temporal relationship to study drug administration, or there was a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

The incidence of AEs was assessed in the combined UC and CD induction and induction/maintenance population by a number of subpopulations, including age, race, sex, baseline disease activity, weight at baseline, creatinine clearance, geographic region, prior use of TNFa, and use of baseline concomitant IBD medications

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As discussed in Section 7.1, adverse event data were pooled across the 2 phase 3 controlled studies which included a Maintenance Trial (Trial C13006 in UC, and Trial C13007 in CD). The patients from these studies are believed to be sufficiently similar that pooling of the data is appropriate.

7.2 Adequacy of Safety Assessments

The safety of vedolizumab was assessed throughout the clinical development program, and clinical trials were overseen by independent data safety monitoring boards. Individual clinical trial protocols outlined safety monitoring and included assessment of AEs, serious AEs, and deaths, monitoring for PML, and the following specific safety related testing:

- Clinical laboratory data:

    - hematology: hematocrit, hemoglobin, platelets, white blood cell count, red blood cell count, absolute basophil count, absolute eosinophil count, absolute lymphocyte count, absolute monocyte count, and absolute neutrophil count
    - clinical chemistry: albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, amylase, bicarbonate, BUN, calcium, creatinine, glucose, lipase, magnesium, phosphorus, total and direct bilirubin, total protein, sodium, potassium, and chloride
    - coagulation: prothrombin time and partial thromboplastin time
- Immunogenicity testing: Blood samples for human antihuman antibodies (HAHA) were obtained at protocol-specified visits to evaluate the potential immunogenicity of vedolizumab.
- JC Viremia: Blood samples for JC viremia were obtained.
- Vital Signs: Heart rate, respiratory rate, blood pressure, and temperature.
- Electrocardiogram: A 12-lead ECG was obtained at rest were obtained and any findings from ECGs collected after study drug administration were to be captured as AEs if there was a clinically significant change from baseline.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The applicant's safety database exceeded the ICH E1A recommendations for drugs that are to be used chronically. Given the potential risk for PML with this class of agents, however, the applicant was recommended to provide a significantly larger safety database. The final recommendation from the Division was that a minimum of 900 patients should have received ≥ 24 infusions with 4 weeks post-infusion follow up, in order to provide an acceptable pre-approval assessment of PML risk in patients with UC and CD.

A total of 3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as of June 27, 2013. This included 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. Across all clinical studies, 2022 patients were exposed to vedolizumab for ≥ 6 months, 1418 patients for ≥ 12 months, 906 for ≥ 24 months, and 407 for ≥ 36 months. Patients were exposed to vedolizumab for a mean of 480.6 days in Phase 2 and 3 studies combined and for a mean of 532.0 days in phase 3 trials combined. Table 26 shows a summary of exposure to vedolizumab by months of exposure and number of infusions.

Table 26 Duration of Exposure to Vedolizumab by Months of Exposure and Number of Infusions (as of 27 June 2013)

Duration	Healthy Subjects	Ulcerative Colitis	Crohn's Disease	Total[a]
At least 1 dose[b]	197	1279	1850	3326
Months of exposure				
≥ 6	0	855	1167	2022
≥ 12	0	588	830	1418
≥ 18	0	485	677	1162
≥ 24	0	428	478	906
≥ 36	0	198	209	407
≥ 48	0	30	10	40
Number of infusions with 4-week follow-up				
≥ 1	193	1261	1826	3280
≥ 6	0	913	1283	2196
≥ 12	0	673	916	1589
≥ 18	0	498	730	1228
≥ 24	0	444	560	1004
≥ 36	0	254	278	532
≥ 48	0	63	53	116

Source: Applicant Submission, Integrated Summary of Safety, 120-day Safety Update, Tables 3-1 and 3-2
[a] Exposure from Studies C13013 and CPH-001 is not included
[b] Dose is defined as administration of any amount of vedolizumab in phase1/2 studies and as administration of ≥ 75% of volume in phase 3 studies

The applicant provided adequate exposure data, based on the Division recommendations to adequately assess PML risk pre-approval. The difference between the number of patients with ≥ 24 months vedolizumab exposure (906) and the number of patients with ≥ 24 vedolizumab infusions (1004) can be explained by 2 reasons. Patients received 2 infusions during the first 2 weeks of induction phase, and patients in the every 4 week cohort received 13 infusions every 12 months.

The Agency was particularly concerned about the impact of prior and concomitant immunosuppressant use and its potential impact on PML risk. Approximately 80% of patients from Phase 3 Studies had prior immunosuppressant use (e.g., azathioprine, 6-mercaptopurine, and methotrexate), and approximately 30% continued immunosuppressants during the trial. The US protocols did not allow concomitant immunosuppressant use beyond the Week 6 induction period. Outside the US, however, there were no restrictions on continued immunosuppressant use. The table below summarizes the number of vedolizumab infusions by prior and concomitant exposure to immunosuppressants. Because patients from the US were required to discontinue immunosuppressants by Week 6, they were classified as no concomitant immunosuppressant use.

Table 27: Vedolizumab Exposure by Concomitant Immunosuppressant Use

Category	Number of Vedolizumab Infusions[a,b]				
	≥ 6 N = 2195	≥ 12 N = 1488	≥ 18 N = 1171	≥ 24 N = 903	≥ 36 N =415
Prior Immunosuppressant Use					
Yes	1757 (80)	1171 (79)	913 (78)	690 (76)	305 (73)
No	438 (20)	317 (21)	258 (22)	213 (24)	110 (27)
Concomitant Immunosuppressant Use[c]					
Yes	608 (28)	449 (30)	356 (30)	268 (30)	107 (26)

No	1587 (72)	1039 (70)	815 (70)	635 (70)	308 (74)

Source: Applicant Submission, Integrated Summary of Safety, Table 2-7
[a] Includes patients from studies C13002, C13004, C13006, 13007, 13008, and 13011; healthy volunteers are not included
[b] Patients had a minimum of 4 weeks follow-up after the last infusion
[c] All US patients are classified as no concomitant immunosuppressant use

Of the patients outside the US categorized as using concomitant immunosuppressant, over half remained on concomitant immunosuppressants for over a year. Duration of concomitant immunosuppressant use is summarized in Table 28, below.

Table 28: Duration of Concomitant Immunosuppressant Use

Duration of Concomitant Immunosuppressants	Ulcerative Colitis N = 282	Crohn's Disease N = 468	Total N = 750
At least 1 dose, n (%)	282 (100)	468 (100)	750 (100)
Months of Exposure			
≥ 3	246 (87)	388 (83)	634 (85)
≥ 6	208 (74)	331 (71)	539 (72)
≥ 12	155 (55)	268 (57)	423 (56)
≥ 18	134 (48)	187 (40)	321 (43)
≥ 24	119 (42)	129 (28)	248 (33)
≥ 36	24 (9)	38 (8)	62 (8)
≥ 48	2 (<1)	1 (<1)	3 (<1)

7.2.2 Explorations for Dose Response

Please see section 6.1.8, Analysis of Clinical Information Relevant to Dosing Recommendations, as well as the Clinical Pharmacology and Pharmacometrics reviews for additional details and assessment of the exposure-response relationship.

The applicant selected 1 induction dose and 2 maintenance dosing regimens to explore in Phase 3 Studies. All patients received 300 mg vedolizumab by intravenous infusion at weeks 0 and 2 for induction. During the maintenance phase, patients received 300 mg vedolizumab IV, either every 4 or every 8 weeks.

Exploration for safety dose-response was undertaken using data from the CD trial C13007 and comparing the adverse events between the 3 Maintenance Trial ITT populations (i.e., placebo, vedolizumab Q8W, and vedolizumab Q4W), as these patients continued to receive blinded study drug throughout the maintenance phase. It is important to note, however, that the placebo ITT population received 2 vedolizumab infusions during induction before being randomized to placebo for the Maintenance Phase.

The adverse event rates were similar between dosing groups. Specifically, 84% of patients in the placebo-ITT group experienced one or more AE, compared to 88% and 84% in the Q8W and Q4W vedolizumab groups, respectively. Fifteen percent (15%) of patients in the placebo group had a serious adverse event and 10% had an adverse event resulting in discontinuation, compared to 18% and 8% in the Q8W vedolizumab group and 16% and 6% in the Q4W group.

When comparing adverse events by specific SOCs, there was no clear trend of higher AEs with the more frequent dosing regimen. Finally, no safety dose-response relationship was seen between dosing regimens for the most common AEs by PT. AEs that occurred in >3% of patients in the combined vedolizumab group are summarized in Table 29, below.

Table 29. Adverse Events That Occurred in > 3% of Patients in the All Vedolizumab Combined Group by Preferred Term by Frequency and Incidence Density – Maintenance Study ITT Population (C13007)

	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)								
	PLA N = 153 TPY = 109.2			VDZ Q8W N = 154 TPY = 108.6			VDZ Q4W N = 154 TPY = 119		
Preferred Term, n (%)	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Crohn's disease	29 (19)	32	0.293	25 (16)	25	0.230	24 (16)	29	0.244
Arthralgia	21 (14)	30	0.275	17 (11)	21	0.193	21 (14)	29	0.244
Pyrexia	23 (15)	26	0.238	18 (12)	18	0.166	29 (19)	35	0.294
Nasopharyngitis	14 (9)	18	0.165	23 (15)	29	0.267	23 (15)	32	0.269
Headache	28 (18)	54	0.495	20 (13)	25	0.230	26 (17)	47	0.395
Nausea	18 (12)	24	0.220	18 (12)	25	0.230	22 (14)	34	0.286
Abdominal pain	18 (12)	27	0.247	15 (10)	19	0.175	19 (12)	29	0.244
Upper respiratory tract infection	6 (4)	6	0.055	7 (5)	7	0.064	13 (8)	15	0.126
Fatigue	9 (6)	11	0.101	11 (7)	14	0.129	11 (7)	14	0.118
Vomiting	13 (8)	16	0.147	9 (6)	16	0.147	8 (5)	9	0.076
Back pain	7 (5)	7	0.064	14 (9)	14	0.129	9 (6)	9	0.076
Urinary tract infection	4 (3)	4	0.037	7 (5)	10	0.092	5 (3)	6	0.050
Anaemia	5 (3)	5	0.046	5 (3)	6	0.055	4 (3)	4	0.034
Cough	4 (3)	7	0.064	7 (5)	7	0.064	7 (5)	7	0.059
Bronchitis	4 (3)	5	0.046	5 (3)	5	0.046	9 (6)	12	0.101
Diarrhoea	13 (8)	14	0.128	6 (4)	7	0.064	6 (4)	7	0.059
Influenza like illness	7 (5)	9	0.082	7 (5)	8	0.074	5 (3)	5	0.042
Dizziness	6 (4)	8	0.073	8 (5)	8	0.074	7 (5)	11	0.092
Sinusitis	4 (3)	4	0.037	5 (3)	6	0.055	8 (5)	11	0.092
Anal abscess	3 (2)	3	0.027	1 (< 1)	1	0.009	4 (3)	5	0.042
Anal fistula	0	0	0.000	2 (1)	2	0.018	5 (3)	7	0.059
Pruritus	3 (2)	3	0.027	3 (2)	3	0.028	4 (3)	4	0.034

Source: Table 79 Pages 308-309 of the C13007 Study Report

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TPY = Total Person Time in Years; VDZ = vedolizumab.

Days for Person Time was defined as (End of study date - first dose date (of induction) + 1).

End of Study Date = Last scheduled dosing date + 16 Weeks for patients who did not continue in the long-term safety study.

End of Study Date = Last scheduled dosing date for patients who did continue in the long-term safety study.

Number of Events: Within the same preferred term, if the start and stop date of multiple events overlap or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.

Incidence Density: Number of Events / Total Person-Time in Years (TPY)

a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT Population at Week 6.

7.2.3 Special Animal and/or In Vitro Testing

Due to the increased risk of PML with natalizumab, an integrin receptor antagonist, other products with similar mechanisms of action may also be at increased risk for this rare but serious demyelinating disease caused by reactivation of latent JC virus infection in the central nervous system (CNS). The applicant completed nonclinical studies aimed at characterizing the binding specificity and selective antagonism of vedolizumab in order to support that vedolizumab has a lower risk of causing PML than natalizumab.

Vedolizumab is a monoclonal antibody that selectively binds to α4β7 integrin, a glycoprotein present on the surface of leukocytes involved in GI mucosal immunity. The ligand of α4β7 integrin is mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is preferentially expressed on the endothelium of GI mucosa. The mechanism of

action of vedolizumab is the inhibition of leukocyte migration to the GI mucosa and interaction with MAdCAM-1. Natalizumab, in contrast, binds to the α4 integrin subunit and thus binds both α4β7 and α4β1, which binds to the endothelial ligand vascular cell adhesion molecule-1 (VCAM-1). An in vitro study utilizing cell lines selectively expressing specific integrins showed that vedolizumab selectively binds to α4β7 and does not bind to α4β1 or αEβ7 integrin. This study also examined the selectivity of vedolizumab for inhibition of α4β7-mediated cell adhesion interactions and showed that vedolizumab inhibited α4β7-MAdCAM-1 and fibronectin and did not inhibit α4β7-VCAM-1, α4β1-VCAM-1, or α4β1-fibronectin-mediated adhesive interactions.

A decrease in immune surveillance of the CNS by T-lymphocytes is hypothesized to contribute to the development of PML. The sponsor conducted a study using an Experimental Autoimmune Encephalomyelitis (EAE) model in Rhesus monkeys (a model of multiple sclerosis; there is no animal model of PML) to assess the impact of vedolizumab and natalizumab on CNS immune surveillance. The results of this study showed that while natalizumab appeared to inhibit immune surveillance of the CNS, vedolizumab had no such effect. In addition, a 3-week comparative immunotoxicity study of natalizumab and vedolizumab was completed in Cynomolgus monkeys. Natalizumab caused a significant increase in lymphocyte populations (e.g., b-lymphocytes, t-helper lymphocytes, etc.), whereas there was no change in these populations in vedolizumab-treated monkeys.

The applicant proposes that their nonclinical data supports the specificity of vedolizumab and the use of vedolizumab does not carry the same increased risk of PML as natalizumab.

See nonclinical pharmacology/toxicology section 4.3 for routine animal and in vitro testing performed and the Nonclinical Review by Tamal Chakraborti, PhD, for additional details.

7.2.4 Routine Clinical Testing

Section 7.2 provides an overview of routine clinical testing performed as part of the safety assessments and the timing and frequency of laboratory and clinical testing are provided in section 5.3.5.

The clinical testing performed as part of routine safety assessments was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Vedolizumab is a humanized monoclonal antibody, and the primary routes of elimination are likely proteolytic degradation and receptor mediated clearance, thus classical in vitro

studies (e.g., human liver microsomes/P450 studies) to investigate PK and vedolizumab's interaction potential were not conducted.

No clinical studies were conducted to specifically evaluate the effect of co-administered drugs on the PK of vedolizumab. The potential for vedolizumab to act as a perpetrator of drug-drug interactions is low, as vedolizumab is an antibody and does not modulate cytokines. The potential for vedolizumab to be impacted by other drugs commonly used in the UC and CD population (e.g., methotrexate, azathioprine, 6-mercaptopurine, and aminosalicylates) was assessed through population PK modeling from phase 3 studies. Vedolizumab clearance was not affected by co-administration of immunomodulators.

See the Clinical Pharmacology Review for additional details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Natalizumab, the only currently approved integrin antagonist, is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis and Crohn's Disease. As a result, integrin antagonists in development have been required to include thorough PML risk identification and minimization programs in their clinical trials and ensure that premarketing patient drug exposure is sufficient to assess the risk for PML before drug approval. The applicant's approach to evaluating for this potential serious risk is described below.

3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as of the cut-off date for inclusion of safety data in the BLA (14March2013), and there were zero cases of PML. This included 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. One thousand and four (1004) patients received ≥ 24 vedolizumab infusions with 4 weeks follow-up. As described in Section 7.2.1, the applicant's pre-approval safety database size was based on Division recommendations that in order to provide a pre-approval assessment of PML risk in patients with UC and CD that would be adequate to take to Advisory Committee for consideration, a minimum of 900 patients should have received ≥ 24 vedolizumab infusions with 4 weeks post-infusion follow up.

The applicant proposes that based on the safety database provided at the time of submission, they have demonstrated that the risk for PML in UC and CD patients taking vedolizumab is less than the risk for PML in patients taking natalizumab. Although direct comparison of vedolizumab to natalizumab is infeasible, the total number of patients and exposure time of vedolizumab is compared to that of natalizumab when the first three PML cases on it were identified. In clinical trials of natalizumab, two PML cases were identified in 1,869 multiple sclerosis (MS) patients and one PML case in 1,043 Crohn's disease (CD) patients. The overall mean duration of exposure to natalizumab was approximately 18 months. This was based on 3 confirmed cases of PML in 3116 patients exposed for this period of time.

The vedolizumab safety database (as of the June 27, 2013 cutoff date) includes 3,326 patients exposed to at least one dose of vedolizumab. Among these patients, 2,830 (85%) patients filled out at least one subjective checklist as part of the RAMP program. The summary statistics (mean and median) for exposure data is shown in Table 30: Vedolizumab Patient ExposureTable 30, below.

Table 30: Vedolizumab Patient Exposure

		All Patients Exposed to Vedolizumab N =3,326	All Patients Exposed to Vedolizumab w/ RAMP N =2,830
No. of Infusions	Mean (SD)	15.4 (14.2)	17.8 (14.1)
	Median (Min-Max)	9.0 (1.0 – 61.0)	13.0 (1.0 – 61.0)
No. of Infusions with > 28 days FU	Mean (SD)	15.0 (14.0)	17.4 (13.9)
	Median (Min-Max)	9.0 (0.0 – 60.0)	13.0 (0.0 – 60.0)
No. of Months Exposure	Mean (SD)	13.6 (13.4)	15.9 (13.3)
	Median (Min-Max)	7.5 (0.0 – 61.3)	11.6 (0.0 – 61.3)

FU=follow-up; SD=standard deviation; Min=minimum value; Max=maximum value

The summary statistic indicates that the mean duration of exposure of all exposed patients (13.6 months) was shorter than the natalizumab mean exposure time of 18 months with a mean of 15 vedolizumab infusions. When limiting all exposed patients to those who have been assessed under the RAMP (2,830 patients), the mean exposure was 15.9 months with a mean of more than 17 vedolizumab infusions. Therefore, the size of the vedolizumab safety database and duration of patient exposure is roughly similar to the natalizumab safety database when the first three PML cases were observed.

A total of 3326 subjects were exposed to vedolizumab during clinical development with 0 confirmed cases of PML, as of 14March2013 (See section 7.3.5 for specific results). The statistical "Rule of Three" states that, in a study where no events are observed, the 95% confidence upper bound for the true event rate is approximately 3/n, where n is the study sample size (or in this case, the total sample size exposed to vedolizumab) *(Jovanovic, B.D. and Levy, P.S. A Look at the Rule of Three. The American Statistician 1997;51(2):137-139)*. Using this principle, based on 0 cases of PML with 3326 exposed, the upper bound of 95% confidence interval (CI) of the risk estimate for PML in vedolizumab treated patients is 0.90/1000. This risk estimate does not take into consideration duration of treatment and includes exposed subjects who received only 1 dose of vedolizumab.

Longer duration of exposure, especially beyond 2 years, is a known risk factor for PML in patients treated with natalizumab. Table 31 below, provided by the Applicant, compares the PML rates in patients treated with natalizumab with the upper bound 95% CI rate based on zero observed PML events in the vedolizumab safety database, stratified by minimum duration of exposure. The applicant proposes they have demonstrated a lower risk for PML with vedolizumab treatment, when considering duration of exposure.

Table 31: PML Incidence Rates and Risk Estimates

Duration of Exposure	Point Estimate Natalizumab PML Rates[a]	Upper Bound 95% CI Rate for 0 Observed Vedolizumab PML Events (27June 2013 data cutoff)
≥ 12 months	3.15/1000	2.1/1000
≥ 18 months	3.40/1000	2.5/1000
≥ 24 months	3.76/1000	3.3/1000

Source: Modified from Table 3.1 in sponsor Submission: Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab
a Bloomgren et al., 2012

The presence of JC virus antibodies and prior immunosuppressant use are also risk factors known to increase the risk of PML in natalizumab treated patients. These risk factors were included in the risk stratification scheme in Table 32 below, by Bloomgren et al., which includes data on natalizumab patients through February 2012. In this table, the effect of natalizumab exposure on risk of PML is modified by duration of exposure, JC virus antibody positivity, and prior immunosuppressant use. The authors estimated the risk for PML was lowest among patients negative for anti-JCV antibodies (0.09 per 1000). The risk for PML was highest among patients who were positive for JCV antibodies, had prior immunosuppressant use (within 24 months of therapy), and had received 25 to 48 months of treatment. The PML risk for this group was 11.1 per 1000. *(Bloomgren G, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med 2012; 366(20):1870-80).*

Table 32: Estimated PML Incidence Rates with Natalizumab Stratified by Risk Factor

Natalizumab Exposure[a]	Anti-JCV Antibody Positive[b]	
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1 – 24 months	0.56/1000	1.6/1000
25 – 48 months	4.6/1000	11.1/1000

Source: Table 3-3 of the applicant's document titled, "Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab" (page 5).
[a] Data beyond 4 years of treatment are limited
[b] Risk in anti-JCV antibody positive patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated MS patients are anti-JCV antibody positive.

The applicant's approach is described as follows. First, all 3,326 patients exposed to at least one vedolizumab dose were stratified by the three known natalizumab PML risk factors: longer duration of treatment (beyond 24 months), prior immunosuppressant use, and positive anti-JCV antibody (Table 33). Approximately 80% of vedolizumab patients had prior immunosuppressant use. For anti-JCV antibody status, the applicant used published rates in the literature, and assumed that approximately 50% of patients to be JC virus antibody positive.

Table 33: Vedolizumab Exposure Stratified by Natalizumab PML Risk Factors

Vedolizumab exposure	Anti-JCV Antibody Positive		Anti-JCV Antibody Negative	Total
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use		
1 – 24 months	333	1330	1663	3326
25 – 48 months	84	334	418	835

Source: Table 3-4 of the applicant's document titled, "Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab" (page 6).

In order to compare the vedolizumab safety database against natalizumab, the applicant applied the risk-stratified PML incidence rates for natalizumab to the vedolizumab exposure stratified by natalizumab PML risk factors. The stratified PML rates in Table 32 were multiplied with the corresponding number of patients in Table 33 and the products were summed up to yield an expected number of PML cases of 6.41 for vedolizumab. Finally, the applicant assumed that PML occurrence among the 3,326 vedolizumab-exposed patients followed a Poisson distribution with a mean of 6.41. Under this assumption, the probability of zero PML cases with the current safety database was very low (~0.1%).

Table 34: Expected PML Cases in Vedolizumab Clinical Development Program, if Risk Similar to Natalizumab (Per the Applicant)

Vedolizumab Exposure	Anti-JCV Antibody Positive	
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1 – 24 months	0.19	2.13
25 – 48 months	0.38	3.71
	Total Expected Cases of PML:	6.41
	Probability of Observing Zero Cases:	0.017

The applicant concluded that if the risk of PML among vedolizumab users were similar to natalizumab users, it would be almost certain that a PML case would occur. Because no PML cases were observed in the vedolizumab safety database, the PML risk is, therefore, lower for vedolizumab than for natalizumab.

7.3 Major Safety Results

CD Comparative Safety

In Clinical Trial C13007, the rates of adverse events were similar in the ITT populations, with 84% of patients in the placebo arm having any adverse event, compared to 88% and 84% in the Q8W and Q4W arms, respectively. The results were similar when comparing the combined vedolizumab group and non-intent-to-treat placebo group. The rates of serious adverse events were similar between the placebo-ITT arm (15%) and each of the vedolizumab-ITT arms (Q8W 18%, Q4W 16%). Also, the rates of adverse events resulting in study discontinuation were similar between the placebo-ITT arm and each of the vedolizumab-ITT arms (Q8W 8%, Q4W 6%). A summary of adverse events from the C13007 Maintenance Safety Population is provided below.

Table 35. Overall Summary of Adverse Events: C13007 Maintenance Safety Population

	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
Adverse Event Category n (%)	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA[b] (from Week 0) N = 148	VDZ Q4W[c] (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Any adverse event	128 (84)	135 (88)	130 (84)	118 (80)	441 (87)	246 (82)	706 (87)
Drug-related adverse event	51 (33)	63 (41)	63 (41)	45 (30)	191 (38)	96 (32)	317 (39)
Adverse event resulting in study discontinuation	15 (10)	12 (8)	9 (6)	14 (9)	70 (14)	29 (10)	91 (11)
Serious adverse event	23 (15)	28 (18)	25 (16)	23 (16)	146 (29)	46 (15)	199 (24)
Serious infection adverse events	5 (3)	6 (4)	9 (6)	4 (3)	30 (6)	9 (3)	45 (6)
Drug-related serious adverse event	4 (3)	5 (3)	6 (4)	2 (1)	24 (5)	6 (2)	35 (4)
Serious adverse event resulting in discontinuation	7 (5)	9 (6)	5 (3)	8 (5)	45 (9)	15 (5)	59 (7)
Deaths	0	1 (< 1)	0	1 (< 1)	3 (< 1)	1 (< 1)	4 (< 1)

Source: Clinical Study Report Study C13007, page 302

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; VDZ = vedolizumab.

a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT Population at Week 6.

b Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.

c Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

UC and CD Comparative Safety

The proportion of patients with at least 1 adverse event was 84%, 78% and 84% in the VDZ/PLA, PLA/PLA, and VDZ/VDZ groups, respectively. More patients had AEs believed to be drug related in the VDZ/VDZ group (36%) compared to the group which received only placebo (28%, PLA/PLA). One death (0.3%) occurred during the clinical trial period in the PLA/PLA group, compared with 5 deaths (0.3%) in the VDZ/VDZ group. Adverse events were reported by a higher proportion of patients in CD Trial C13007 (87% VDZ/VDZ; 80% PLA/PLA) compared to UC Trial C13006 (80% VDZ/VDZ; 77% PLA/PLA). Similarly, there were a higher proportion of patients reporting serious AEs in C13007 (24% VDZ/VDZ; 16% PLA/PLA) compared to C13006 (12% VDZ/VDZ; 11% PLA/PLA). Table 36 provides an overall summary of adverse events for the combined UC and CD comparative safety population.

Table 36: Overall Summary of Adverse Events – UC and CD Comparative Safety Population

Adverse Event Category, n (%)	VDZ/PLA[a] N = 279	PLA/PLA[b] N = 297	VDZ/VDZ[c] N = 1434
Any AE	234 (84)	232 (78)	1203 (84)
Any treatment related AE	91 (33)	83 (28)	517 (36)
AE resulting in discontinuation	30 (11)	30 (10)	127 (9)
Serious AE	43 (15)	40 (13)	276 (19)
Serious infection	9 (3)	8 (3)	57 (4)
Drug-related Serious AE	8 (3)	5 (2)	48 (3)
Serious AE resulting in discontinuation	14 (5)	14 (5)	75 (5)
Death	0	1 (<1)	5 (<1)

Source: Applicant Submission, Integrated Summary of Safety, Table 4-17
[a] ITT placebo group includes patients who received vedolizumab during induction and were randomized to placebo during the Maintenance Phase
[b] Non-ITT placebo group includes patients who received placebo during the Induction Phase and continued to receive placebo during the Maintenance Phase. These patients are not included in the combined UC and CD group above
[c] Combined VDZ group includes responders to VDZ induction who were randomized to VDZ treatment (Q4W or Q8W) at Week 6 and patients who received VDZ during the Induction Phase but did not achieve clinical response at Week 6 and continued to receive vedolizumab Q4W during the Maintenance Phase

Long-Term Safety

In considering the long-term safety of vedolizumab, AEs were analyzed across Trial C13008, as well as across qualifying studies for rollover patients. As of June 27, 2013, the overall incidence of AEs was 91% (93% in CD and 89% in UC).. The incidence of SAEs was 27% and was also higher among CD patients (31%) than UC patients (20%). Results from a retrospective observational cohort study performed on data from an external administrative database (HealthCore Integrated Research Database [HIRD^{SM}]) were used to provide a benchmark for evaluation of long-term AEs. The database included a broad representation of patients with IBD on a variety of therapies, including biological agents. Adverse event rates per 1000 person years were comparable between C13008 and the HIRD^{SM} database results.

Reviewer comments: The overall rate of adverse events was similar between the treatment groups in the UC and CD comparative safety population, as were the rates of adverse events leading to discontinuation. There were somewhat higher rates of adverse events and serious adverse events reported among CD patients, however, this may be related to the underlying disease process and higher frequency of extraintestinal symptoms and complications of Crohn's disease.

7.3.1 Deaths

There were 13 deaths total across all controlled and uncontrolled studies in UC and CD during participation in clinical studies. All of the deaths occurred during Phase 3 studies, 6 during placebo controlled trials C13006 and C13007 and 7 during open-label long term extension trials. One patient with UC receiving vedolizumab died during the Induction Phase of Clinical Trial C13006 (Cohort 2) and 5 CD patients died in Study 13007, 1 from the PBO/PBO group and the other 4 from vedolizumab groups. Table 37 below summarizes the number of deaths in patients occurring in the placebo controlled trials, by exposure to vedolizumab.

Table 37: Summary of Deaths from Randomized Controlled Trials

Vedolizumab Exposure	Died	Survived	Total
Exposed[a]	5	1708	1713
Unexposed	1	296	297
Total	6	2004	2010

[a] The exposed population includes patients from the combined vedolizumab group and ITT-placebo group.

Of the 7 patients who died in the open-label extension trial C13008 through June 27, 2013, 3 had UC and 4 CD. The events leading to death among the UC patients were respiratory failure, cerebrovascular accident, and pulmonary embolism, and none were assessed by the investigator to be related to the study drug. Among the CD patients, traumatic intracranial hemorrhage, hepatic neoplasm, suicide, and sepsis led to patient deaths. Only the hepatic neoplasm was assessed as potentially related to the study

drug by the study site investigator. Table 38 below summarizes the deaths in the UC population which occurred during participation in clinical studies, and Table 39 summarizes the deaths in the CD population.

Table 38: Narratives of Deaths in UC Patients

Patient ID	Treatment Group	Days after first dose/last dose	Primary cause of death/narrative	Assessment of relatedness by investigator/ FDA reviewer
C13006				
C13006 - 46007-608	Cohort 2 VDZ	14/14	66-year-old male patient from Russia with a history of ischemic heart disease who received a single 300 mg infusion of vedolizumab for induction. The patient died 14 days after infusion due to sudden cardiac death.	Not related/ not related
C13008				
C13006-50016-602	C13006: VDZ induction/ PBO maintenance C13008: VDZ	332/50	49-year-old female from South Africa with a history of Hashimoto's thyroiditis and hypothyroidism who received vedolizumab induction and placebo maintenance in Trial C13006. Pt received 2 vedolizumab infusions and 7 placebo infusions in C13006 before being discontinued due to lack of efficacy. Patient enrolled in Trial C13008, and after her second vedolizumab infusion she was hospitalized with worsening UC requiring proctocolectomy. Treatments included IV hydrocortisone, and her exacerbation was considered resolved. She was readmitted for a scheduled colectomy. 9 days following surgery she developed an acute abdomen and septic shock and subsequently developed respiratory failure and died.	Not related/ not related
C13006-58023-603	C13006: VDZ induction/ VDZ maintenance C13008: VDZ	195/111	70-year-old female patient from the US with multiple medical conditions including diabetes, hypertension, hyperlipidemia, GERD, and asthma, who received 4 infusions of double-blind vedolizumab in Trial C13006. She was discontinued from the study due to lack of efficacy and enrolled in Trial C13008 for open label vedolizumab. She received 1 dose of open-label vedolizumab and 23 days later experienced a nonserious event of esophageal candidiasis. The patient received no additional doses of vedolizumab following the event, and 13 days later (36 days after last vedolizumab dose) was hospitalized for worsening UC. She underwent a laparoscopic panproctocolectomy, permanent ileostomy, cystopanendoscopy and bilateral ureteral catheterization. Twelve days following surgery she underwent cardiac catheterization with placement of 4 stents for severe myocardial ischemia. She was discharged to rehabilitation and her course was further complicated by pneumonia, nonsustained episodes of ventricular tachycardia, and two cerebrovascular accidents. She died 111 days after her last vedolizumab infusion.	Not related/ not related
C13008-46210-005	VDZ	883/16	72-year-old male patient with a history of coronary heart disease, hypertension, diabetes, and asthma who received 4 doses of vedolizumab 10mg/kg in Trial C13002 and 12 doses of 2mg/kg in Trial C13004 prior to enrolling in C13008. Patient received one 300mg vedolizumab infusion in C13008 and 14 days later was hospitalized with a pulmonary embolism and died.	Not related/ not related

Source: Applicant Submission, Integrated Summary of Safety

Table 39: Narratives of Deaths in CD Patients

Patient ID	Treatment Group	Days after first dose/last dose	Primary cause of death/narrative	Assessment of relatedness by investigator/ FDA reviewer
C13007				
C13007-24001-705	VDZ Q8W	260/45	28-year old male from India who received 5 doses of VDZ in C13007. The patient was hospitalized with an exacerbation of CD and sepsis 22 days after his last infusion. A CT showed pneumoperitoneum, however, the investigator managed the patient medically. He developed respiratory failure and was placed on a ventilator. His condition continued to deteriorate, and he died 45 days after his last dose of medication.	Related/ not related
C13007-37005-703	Non-ITT PBO	Placebo/ placebo	75-year old diabetic from New Zealand who received 8 doses of placebo and was hospitalized with CD exacerbation and discontinued from the study. 48-days after his last dose he experienced cardiac arrest and died.	Not related/ not related
C13007-24028-708	VDZ Q4W	98/28	30-year old male from India with a history of pulmonary emboli, DVT, anemia, and malnourishment received 4 doses of VDZ in 13007. Twenty-seven days after his 4th dose he was hospitalized with acute intestinal obstruction and was found to have bronchopneumonia. He subsequently developed of septic shock and died with cardiac arrest.	Related/ not related
C13007-58025-702	VDZ Q4W	97/6	46-year old female from the US with a history of depression, previous suicide attempt, TMJ syndrome, and hypothyroidism who received 5 infusions of VDZ. Six days following her 5th infusion she died from an intentional drug overdose.	Not related/ not related
C13007-58045-730	VDZ Induction	88/75	23-year old male from the US who received 2 doses of VDZ during induction. Seventy-five days after his second dose, the patient's mother was flushing his TPN line when he reported chest pain and shortness of breath. The patient died in transit to the hospital. Autopsy revealed lymphocytic myocarditis and perivascular foreign-body type granulomatous inflammation of the lungs, consistent with IV injection of medications intended for oral administration.	Not related/ not related
C13008				
C13007-07113-703	C13007: PBO induction/ PBO maintenance C13008: VDZ	387/23	63- year old male from Canada who received placebo in C13007 and subsequently enrolled in C13008. Sixteen days after his 14th dose of VDZ in C13008, the patient fell down the stairs, suffered an intracranial hemorrhage, and died. The patient's family reported that he had been drinking before the event.	Not related/ not related

Patient ID	Treatment Group	Days after first dose/last dose	Primary cause of death/narrative	Assessment of relatedness by investigator/ FDA reviewer
C13007-12013-702	C13007: VDZ induction/ VDZ maintenance C13008: VDZ Q4W	1193/58	51-year old female from the Czech republic who was diagnosed with hepatocellular carcinoma after approximately 3 years of vedolizumab exposure. She had a family history of hepatic carcinoma but was negative for hepatitis B and C. Her LFTs were normal throughout the study, excluding 1 isolated elevation of ALT of 42 U/L about 9 months before presentation. She presented with epigastric pain and was diagnosed following CT and histopathology. She died 2 weeks later.	Related/ Not related
C13007-12017-705	C13007: VDZ induction/PBO maintenance C13008: VDZ	380/98	38-year old male from the Czech republic with a history of depression for which he was receiving fluvoxamine committed suicide 99 days after his 5th infusion of vedolizumab in C13008.	Not related/Not related
C13011-33003-901	C13011: PBO C13008: VDZ	125/125	A 32-year old male from Malaysia who received a single dose of VDZ in C13008. Approximately 2 months after receiving VDZ he was hospitalized with a CD exacerbation and experienced sepsis. His condition deteriorated and the patient died during the hospitalization.	Not related/ not related

Source: Applicant Submission, Integrated Summary of Safety

After clinical trial completion, there were additional deaths in patients who previously participated in controlled phase 3 trials. Specifically:

Patient C13006-28011-602 was a 32 year-old white male patient from Italy who was enrolled in Cohort 2 and received a single infusion of vedolizumab during Induction before withdrawing from the trial. One hundred ten days after his single dose of vedolizumab, he underwent a total colectomy with ileal pouch anastamosis for ulcerative colitis. The patient developed peritonitis requiring a second surgery and subsequently experienced respiratory failure and sepsis. He died from cardiac arrest related to sepsis and multiple organ failure.

Patient C13006-53003-601 was a 32 year-old white male from Switzerland who received blinded vedolizumab during the Induction Phase and achieved clinical response. He was randomized to vedolizumab Q8W during the Maintenance Phase and received 9 additional infusions (5 vedolizumab and 4 placebo) before discontinuing from the trial due to a lack of efficacy. Seventy-one days after his final infusion, biopsies of the descending colon revealed moderately differentiated adenocarcinoma, and the patient underwent total colectomy and subsequent chemotherapy to treat multiple metastases. The patient died 552 days after his final dose of vedolizumab.

Patient C13007-04009-709 was a 52-year-old female from Belgium. She died nearly 2 years after the last dose of vedolizumab of cardiorespiratory arrest. The patient's medical history included chronic obstructive pulmonary disease. The patient received 5 doses of open-label vedolizumab and was discontinued from the study at the request of the patient. It was reported that the patient had a severe cold and suffered sudden

cardiopulmonary arrest 660 days after her last dose of study drug. The investigator indicated that no autopsy was performed and considered the event not related to study treatment.

FDA Reviewer Comments: When comparing the risk of death in placebo controlled trials, the risk appears to be similar in vedolizumab exposed patients and unexposed patients; however, as previously stated, given the low event rate, any interpretation of these comparisons should be viewed with caution. None of the deaths in UC patients were assessed to be related to study drug, as determined by study investigators and confirmed by the FDA reviewer. In C13007, 2 deaths were assessed as possibly related to study drug by the investigator. Both of these deaths were the result of exacerbation of CD and sepsis/infection. The FDA reviewer believes these CD exacerbations were not likely related to study drug, rather exacerbations due to lack of drug effect in these patients, and therefore would not categorize them as related to study drug. One additional death in a CD patient participating in C13008 was assessed as possibly related to study drug. This was a case of hepatocellular carcinoma occurring approximately 3 years after initiation of vedolizumab. The FDA reviewer believes it is not plausible this death was related to study drug, given the mechanism of action for vedolizumab. Given the low incidence rate, it is difficult to comment further on any potential relationship. Adverse events, including SAEs and deaths, should continue to be collected and assessed in the postmarketing setting.

7.3.2 Nonfatal Serious Adverse Events

CD Comparative Safety

In Trial C13007, maintenance ITT population, there were a similar proportion of patients in the placebo group who experienced at least 1 SAE compared with the vedolizumab treatment groups (15% placebo, 18% Q8W, 16% Q4W). The proportion of patients with at least one SAE was higher in the combined vedolizumab group than the non-ITT placebo group (24% vs. 16%). SAEs determined by the investigator to be drug related occurred infrequently and there were no differences seen between treatment arms in the ITT groups (placebo 3%, VDZ Q8W 3%, VDZ Q4W 4%); SAE's determined by the investigator to be drug related were higher in the combined vedolizumab group (4%) than the non-ITT placebo group (1%).

The most frequent non-fatal SAE in the Maintenance Trial ITT group was Crohn's disease, which occurred in 5% of placebo patients, 8% of Q8W vedolizumab and 4% of Q4W vedolizumab patients. Crohn's disease was reported in 120 patients in the Maintenance Phase overall, and the highest rates were reported in the non-ITT groups; 13 placebo patients (9%) and 81 non-ITT vedolizumab patients (16%) reported Crohn's disease as a serious AE.

SAEs in the Infections and Infestations SOC were seen in 3-6% of patients. Higher rates of SAEs in the Infections and Infestations SOC were reported in the VDZ Q4W ITT arm (6%) than the VDZ Q8W ITT arm (4%) and the PLA ITT arm (3%). Higher rates of SAEs in the Infections and Infestations SOC were reported in the VDZ Q4W non-ITT group (6%) than the PLA non-ITT group (3%).

SAEs which were reported by greater than 1% of patients by PT are summarized in the tables below.

Table 40: Summary of SAEs that occurred in >1% of Patients in any Vedolizumab Group, by SOC and PT - Maintenance Study ITT Population (C13007)

	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)								
	PLA N = 153 TPY = 109.2			VDZ Q8W N = 154 TPY = 108.6			VDZ Q4W N = 154 TPY = 119		
Primary System Organ Class, n (%) Preferred Term	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Patients with at least 1 serious adverse event	23 (15)	46	0.421	28 (18)	31	0.285	25 (16)	31	0.261
Gastrointestinal disorders	18 (12)	29	0.266	18 (12)	18	0.166	11 (7)	13	0.109
Crohn's disease	8 (5)	9	0.082	12 (8)	12	0.110	6 (4)	6	0.050
Infections and infestations	5 (3)	8	0.073	6 (4)	7	0.064	9 (6)	10	0.084
Anal abscess	0	0	0.000	1 (< 1)	1	0.009	2 (1)	2	0.017

Source: Table 90 on Page 363 of the C13007 Study Report

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; Q8W = dosing every 8 weeks; TPY = Total Person-Time in Years; VDZ = vedolizumab.

Days for Person-Time was defined as (End of study date - first dose date (of induction) + 1).

End of Study Date = Last scheduled dosing date + 16 Weeks for patients who did not continue in the long-term safety study.

End of Study Date = Last scheduled dosing date for patients who did continue in the long-term safety study.

Number of Events: Within the same preferred term, if the start and stop date of multiple events overlap or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.

Incidence Density: Number of Events / Total Person-Time in Years (TPY)

a Maintenance ITT includes patients who received vedolizumab during the Induction Phase, determined to be responders to induction therapy, and were randomized to the Maintenance ITT Population at Week 6.

Table 41: Summary of SAEs that occurred in >1% of Patients in any Vedolizumab Group, by SOC and PT - Maintenance Non-ITT Groups and Combined Vedolizumab Group (C13007)

	Maintenance Non-ITT						Combined					
	PLA[a] (from Week 0) N = 148 TPY = 82.3			VDZ Q4W[b] (Week 6 Nonresponders) N = 506 TPY = 322.4			PLA N = 301 TPY = 263.2			VDZ N = 814 TPY = 700.8		
Primary System Organ Class, n (%) Preferred Term	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Patients with at least 1 serious adverse event	23 (16)	30	0.365	146 (29)	221	0.685	46 (15)	76	0.397	199 (24)	283	0.515
Gastrointestinal disorders	18 (12)	20	0.243	102 (20)	124	0.385	36 (12)	49	0.256	131 (16)	155	0.282
Crohn's disease	13 (9)	14	0.170	81 (16)	90	0.279	21 (7)	23	0.120	99 (12)	108	0.196
Infections and infestations	4 (3)	4	0.049	30 (6)	34	0.105	9 (3)	12	0.063	45 (6)	51	0.093
Anal abscess	1 (< 1)	1	0.012	13 (3)	13	0.040	1 (< 1)	1	0.005	16 (2)	16	0.029

Source: Table 91 on Page 364 of the C13007 Study Report

Abbreviations: ITT = intent-to-treat; PLA = placebo; Q4W = dosing every 4 weeks; TPY = Total Person-Time in Years; VDZ = vedolizumab.

Days for Person-Time was defined as (End of study date - first dose date (of induction) + 1).

End of Study Date = Last scheduled dosing date + 16 Weeks for patients who did not continue in the long-term safety study.

End of Study Date = Last scheduled dosing date for patients who did continue in the long-term safety study.

Number of Events: Within the same preferred term, if the start and stop date of multiple events overlap or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events.

Incidence Density: Number of Events / Total Person-Time in Years (TPY)

a Maintenance Non-ITT placebo includes patients who received placebo during the Induction Phase and were assigned to continue placebo during the Maintenance Phase.

b Maintenance Non-ITT vedolizumab Q4W includes patients who received vedolizumab in the Induction Phase, did not achieve clinical response at Week 6, and were assigned to receive vedolizumab Q4W during the Maintenance Phase.

The proportion of patients with SAEs in the patients with baseline immunomodulator and/or corticosteroid use was also analyzed in C13007. Patients receiving vedolizumab with baseline concomitant corticosteroids and/or immunomodulators did not have increased rates of SAEs, in comparison to patients not on these medications. SAEs which were reported by greater than 1 person are summarized below, based on concomitant immunosuppressant and/or corticosteroid use. No trends were identified.

Table 42: SAEs that occurred in ≥ 4 Patients by Concomitant Corticosteroid and/or Immunosuppressant Use, by PT - Maintenance Phase Safety Population (C13007)

	Combined							
	PLA N=302				VDZ N=813			
Preferred Term n (%)	Neither COR nor IMM N=101	COR Only N=101	IMM Only N=48	COR+IMM N=52	Neither COR nor IMM N=263	COR Only N=280	IMM Only N=133	COR+IMM N=137
Patients Using Concomitant Therapy	37 (37)	45 (45)	20 (42)	19 (37)	122 (46)	117 (42)	59 (44)	61 (45)
Nasopharyngitis	10 (10)	7 (7)	4 (8)	3 (6)	39 (15)	25 (9)	15 (11)	21 (15)
Upper respiratory tract infection	3 (3)	8 (8)	3 (6)	3 (6)	14 (5)	20 (7)	11 (8)	9 (7)
Urinary tract infection	4 (4)	3 (3)	0	0	10 (4)	10 (4)	5 (4)	10 (7)
Bronchitis	5 (5)	2 (2)	1 (2)	1 (2)	13 (5)	12 (4)	4 (3)	4 (3)
Sinusitis	2 (2)	2 (2)	0	1 (2)	10 (4)	12 (4)	2 (2)	5 (4)
Anal abscess	1 (<1)	2 (2)	1 (2)	2 (4)	8 (3)	8 (3)	6 (5)	6 (4)
Influenza	4 (4)	2 (2)	1 (2)	2 (4)	10 (4)	7 (3)	1 (<1)	3 (2)
Gastroenteritis	3 (3)	2 (2)	2 (4)	1 (2)	4 (2)	9 (3)	1 (<1)	1 (<1)
Pharyngitis	0	1 (<1)	1 (2)	2 (4)	7 (3)	6 (2)	1 (<1)	1 (<1)
Gastroenteritis viral	1 (<1)	1 (<1)	1 (2)	0	4 (2)	6 (2)	1 (<1)	1 (<1)
Oral herpes	1 (<1)	2 (2)	3 (6)	0	5 (2)	1 (<1)	2 (2)	3 (2)
Pneumonia	1 (<1)	1 (<1)	1 (2)	0	2 (<1)	4 (1)	2 (2)	1 (<1)
Folliculitis	0	1 (<1)	0	0	3 (1)	3 (1)	2 (2)	1 (<1)
Abdominal abscess	1 (<1)	1 (<1)	0	0	3 (1)	2 (<1)	0	2 (1)
Respiratory tract infection	1 (<1)	1 (<1)	0	0	0	1 (<1)	2 (2)	4 (3)
Vulvovaginal mycotic infection	0	2 (2)	0	0	0	4 (1)	2 (2)	1 (<1)
Furuncle	3 (3)	1 (<1)	0	1 (2)	3 (1)	2 (<1)	1 (<1)	0
Ear infection	0	0	0	0	4 (2)	1 (<1)	0	1 (<1)
Oral candidiasis	1 (<1)	1 (<1)	1 (2)	1 (2)	3 (1)	1 (<1)	1 (<1)	0
Rhinitis	0	1 (<1)	0	2 (4)	1 (<1)	1 (<1)	1 (<1)	2 (1)
Cystitis	2 (2)	0	0	0	1 (<1)	2 (<1)	0	2 (1)
Lower respiratory tract infection	0	1 (<1)	0	0	4 (2)	1 (<1)	0	0
Fungal infection	1 (<1)	0	0	0	3 (1)	1 (<1)	0	0
Herpes zoster	0	1 (<1)	0	0	1 (<1)	1 (<1)	2 (2)	0
Vulvovaginal candidiasis	1 (<1)	0	0	0	0	2 (<1)	1 (<1)	1 (<1)
Subcutaneous abscess	0	0	0	0	2 (<1)	0	1 (<1)	1 (<1)
Cellulitis	1 (<1)	2 (2)	0	1 (2)	2 (<1)	0	1 (<1)	0
Tooth abscess	0	3 (3)	0	0	1 (<1)	2 (<1)	0	0
Herpes simplex	1 (<1)	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Hordeolum	0	1 (<1)	0	0	1 (<1)	0	1 (<1)	1 (<1)

Neither COR nor IMM = no concomitant immunosuppressant or corticosteroid use, COR only = concomitant corticosteroids only, IMM only = concomitant immunosuppressants only, COR and IMM = concomitant corticosteroids and immunosuppressants
Source: Clinical Study Report Study C13007, Table 14.4.2.6EM

Similarly, when assessing SAEs in the subgroup of patients in C13007 who were prior TNFa antagonist failures, the only SAEs that occurred in > 1% of the combined vedolizumab group were Crohn's disease (5% ITT placebo; 14% non-ITT placebo; 14% combined vedolizumab) and anal abscess (0% ITT placebo; 0% non-ITT placebo ;2% combined vedolizumab).

UC and CD Comparative Safety

The only serious AEs which occurred in ≥ 1% of the combined vedolizumab population were Crohn's disease, ulcerative colitis, and anal abscess. The proportion of patients reporting at least 1 SAE was larger in the VDZ/VDZ group than in the PLA/PLA group. This was largely driven by SAE reporting in C13007. There was a higher overall rate of serious adverse events in Trial C13007 for Crohn's disease, with 199 (24%) of patients in the VDZ/VDZ group reporting at least 1 SAE, compared to 23 (16%) in the PLA/PLA group. The most commonly reported SAEs in C13007 were Crohn's disease and anal abscess which were reported by 99 (12%) and 16 (2%) in the combined vedolizumab group compared to 13 (9%) and 1 (<1%) in the non-ITT placebo group. A summary of SAEs occurring in ≥ 1% of the combined vedolizumab population is provided below.

Table 43: SAEs Occurring in ≥ 1% of the combined vedolizumab population, by SOC and PT

System Organ Class, n (%) Preferred Term	VDZ/PLA N = 279	PLA/PLA N = 297	VDZ/VDZ N = 1434
Patients with at least 1 SAE	43 (15)	40 (13)	276 (19)
Gastrointestinal disorders	27 (10)	30 (10)	180 (13)
Crohn's disease	8 (3)	13 (4)	99 (7)
Ulcerative colitis	7 (3)	10 (3)	47 (3)
Infections and infestations	9 (3)	8 (3)	57 (4)
Anal abscesses	0	1 (<1)	18 (1)

Source: Applicant Submission, Integrated Summary of Safety
[a] patients received vedolizumab during Induction Phase and were randomized to placebo for the Maintenance Phase
[b] patients received placebo during the Induction Phase and continued to receive placebo during Maintenance Phase
[c] includes the ITT Q8W, ITT Q4W, and the non-ITT vedolizumab Q4W groups.

Results were similar when looking at the subgroup of patients who had previously failed TNFα antagonists. Serious AEs were reported in 15%, 17%, and 21% of patients in the ITT placebo, non-ITT placebo, and combined vedolizumab groups. Crohn's disease and ulcerative colitis remained the most commonly reported SAEs, with rates similar to those seen in the general study population.

Long-Term Safety

At least 1 SAE was reported for 18% of UC patients and 29% of CD patients when analyzed across Trial C13008, as well as across qualifying studies for rollover patients. The time adjusted incidence of SAEs per 1000 person-years was also higher for CD than UC patients (187.83 patients/1000 person-years vs 97.34 patients/1000 person years, respectively). Gastrointestinal disorders were the most commonly reported SAEs. When analyzing SAE rates by duration of vedolizumab exposure, there was no apparent increased frequency seen with longer periods of use, as shown in Table 44 below, which summarizes the most commonly reported SAEs by months of vedolizumab exposure.

Table 44: Summary of SAEs by Months of Exposure

	Months of exposure						
SOC HLT, n(%)	0 to < 3 N = 2830	3 to < 6 N = 2722	6 to <12 N = 2435	12 to <18 N = 1600	18 to <24 N = 1203	24 to <36 N = 980	36 to <48 N = 341
Patients with at least 1 SAE	251 (9)	211 (8)	218 (9)	119 (7)	60 (5)	75 (8)	17 (5)
Gastrointestinal disorders	146 (5)	137 (5)	139 (6)	64 (4)	38 (3)	35 (4)	9 (3)
Gastrointestinal inflammatory disorders NEC	84 (3)	82 (3)	59 (2)	28 (2)	21 (2)	8 (<1)	2 (<1)
Colitis (excl infective)	29 (1)	28 (1)	37 (2)	17 (1)	8 (<1)	8 (<1)	2 (<1)
Gastrointestinal and abdominal pain	9 (<1)	4 (<1)	10 (<1)	7 (<1)	2 (<1)	10 (1)	3 (<1)
Infections and infestations	53 (2)	52 (2)	46 (2)	20 (1)	12 (<1)	17 (2)	5 (1)
Abdominal and gastrointestinal infections	26 (<1)	20 (<1)	23 (<1)	9 (<1)	6 (<1)	5 (<1)	3 (<1)
Lower respiratory tract and lung infections	7 (<1)	5 (<1)	3 (<1)	0	1 (<1)	4 (<1)	1 (<1)

Source: Applicant Submission, Integrated Summary of Safety, Table 18.1.2.4B

Reviewer comments: Serious adverse events were reported in 19% of patients taking vedolizumab compared to 13% of patients who received placebo only. The more commonly reported serious adverse events were largely related to the underlying disease and not likely to be related to drug treatment specifically. In the UC population, these SAEs occurred with similar frequency between treatment arms, though they did occur more commonly in patients treated with vedolizumab among CD patients.

7.3.3 Dropouts and/or Discontinuations

CD Comparative Safety

Patients who discontinued from Trial C13007 for any reason were to return to clinic at the earliest opportunity to complete the Early Termination visit. This visit was identical to the Week 52 assessment and included a physical examination, PML checklist, and appropriate labwork. These patients were also to have completed the Week 66/Final Safety visit and complete a 2-year follow-up survey. Patients with adverse events determined by the investigator as related to study drug were not eligible for Trial C13008, however those with AEs determined to be unrelated were eligible for enrollment in the long-term safety study.

Overall, a high percentage of patients discontinued from Trial C13007, with the highest proportion discontinuing from the non-ITT placebo arm (72%) followed by combined vedolizumab arm (61%) and ITT-placebo arm (58%), respectively. The majority of patients discontinued due to lack of efficacy (42% ITT-placebo, 54% non-ITT placebo, and 39% combined vedolizumab, respectively), and these discontinuations happened primarily during the Maintenance Phase of the Clinical Trial. See Section 6.1.3 Patient Disposition for additional details.

Similar proportions of patients discontinued from Study C13007 for an adverse event from the placebo groups than from the vedolizumab groups. Fifteen (10%) patients in the ITT placebo arm discontinued for an AE, compared to 12 (8%) patients in the ITT VDZ Q8W group and 9 (6%) patients in the ITT VDZ Q4W group. Similarly, 14 patients (9%) discontinued from the non-ITT placebo group for an AE, compared to 92 patients (11%) from the combined VDZ group. The most commonly reported AE leading to discontinuation in any treatment arm was Crohn's disease which was reported at rates of 5% in the ITT placebo group, 7% in the non-ITT placebo group, and 5% in the combined vedolizumab group. The only other AE leading to study discontinuation that occurred in more than 1% of patients in each treatment group was abdominal pain (1% in ITT placebo group; 0% in non-ITT placebo group, and <1% in the combined vedolizumab group). Adverse events leading to discontinuations in at least 1% of patients are summarized in. This table includes all patients who discontinued at any time from Week 0.

Table 45: C13006 Adverse Events Leading to Discontinuation in ≥1% of Patients from any Treatment Group

	Maintenance Study ITT			Non-ITT[a]		Combined	
Subject Disposition	Placebo N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA N = 148	VDZ Q4W N = 506	PLA N = 301	VDZ N = 814
Discontinued Study (reason)	89 (58)	81 (53)	72 (47)	106 (72)[b]	343 (68)[c]	195 (65)	496 (61)
Lack of Efficacy	64 (42)	58 (38)	48 (31)	80 (54)	208 (41)	144 (48)	314 (39)
Adverse Event (type)	15 (10)	12 (8)	9 (6)	14 (9)	71 (14)	29 (10)	92 (11)
Crohn's disease	8 (5)	6 (4)	3 (2)	11 (7)	34 (7)	19 (6)	43 (5)
Abdominal Pain	2(1)	0	0	0	1 (<1)	2 (<1)	1 (<1)

Source: Modified from Table 44 on Page 196 of the C13007 Study Report and Table 95 on Pages 379-382 of the C13007 Study Report

UC and CD Comparative Safety

The overall proportion of patients with at least 1 AE leading to clinical trial discontinuation was similar between the placebo groups and VDZ/VDZ groups. The most common AEs resulting in study discontinuation from the combined group were ulcerative colitis and Crohn's disease. No other adverse events led to discontinuation in at least 1% of patients from the combined safety populations. Adverse events leading to discontinuation in the combined safety population are summarized in Table 46.

Table 46: Adverse Events Leading to Discontinuation in ≥1% of the Combined Safety Population

Adverse Event Category	VDZ/PLA[a]	PLA/PLA[b]	VDZ/VDZ[c]
N	279	297	1434
Patients with at least 1 AE resulting in study discontinuation (%)	30 (11)	30 (10)	127 (9)
Gastrointestinal disorders	22 (8)	26 (9)	78 (5)
Crohn's disease	8 (3)	11 (4)	43 (3)
Ulcerative colitis	10 (4)	14 (5)	18 (1)

Source: Applicant Submission, Integrated Summary of Safety, Table 4-45

[a] patients who received vedolizumab during Induction Phase and were randomized to placebo for the Maintenance Phase

[b] patients who received placebo during Induction Phase and continued to receive placebo during Maintenance Phase

[c] includes the ITT vedolizumab groups and the non-ITT vedolizumab group

7.3.4 Significant Adverse Events

These are discussed in section 7.3.5 Submission-Specific Primary Safety Concerns.

7.3.5 Submission Specific Primary Safety Concerns

Vedolizumab is being proposed for the treatment of patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist. Treatment with TNF antagonists has been associated with a variety of serious adverse events including opportunistic infections, reactivation of tuberculosis, malignancies, and hypersensitivity reactions. In addition,

neurological adverse events, specifically related to the potential risk for PML, were primary safety concerns in this submission.

Infection-related Events

MAdCAM-1 binding sites are predominantly in the gastrointestinal tract but are also distributed in the nasopharyngeal, oropharyngeal and vaginal tissue. Based on this distribution, an increased rate of upper respiratory tract, esophageal, and vaginal infections may be expected – this is believed to be related to the known mechanism of action and targets of vedolizumab and not related to immunosuppression. Similarly, given vedolizumab's mechanism of action and inhibition of lymphocyte trafficking to the GI tract there is a risk of increased GI infections, as well as systemic infections from enteric pathogens such as Listeria, Salmonella, and C. difficile and Campylobacter.

CD Comparative Safety:

In C13007, a higher proportion of patients reported at least 1 infection in the ITT combined vedolizumab group than in the non-ITT placebo group and similar to the ITT placebo group (42% ITT placebo; 39% non-ITT placebo; 44% combined vedolizumab). In the infections and infestations SOC, the most commonly reported HLT was upper respiratory tract infections (19% ITT placebo; 18% non-ITT placebo; 23% combined vedolizumab); this appears to have driven the difference in frequency of infections between groups. Other infection HLTs reported in ≥ 5% of patients in the combined vedolizumab arm were abdominal and gastrointestinal infections (8%), lower respiratory tract and lung infections (6%), and urinary tract infections (5%). A similar proportion of patients reported these events in each of the treatment arms. The proportion of patients with infection was slightly higher in the ITT vedolizumab Q8W and the ITT vedolizumab Q4W arms than the ITT placebo arm (46% ITT vedolizumab Q8W; 45% ITT vedolizumab Q4W; 42% ITT placebo); however, no significant differences were noted when comparing specific HLTs.

Infections of specific interest with vedolizumab use include Clostridium difficile, candida, and herpes infections. These cases occurred at similar frequencies in vedolizumab treated patients and placebo patients; all were considered mild to moderate in intensity, most resolved by the end of the study, and only 2 herpes-related infections resulted in study discontinuation (1 case of herpes zoster and 1 case of oral herpes) and 1 Clostridium difficile infection resulted in study discontinuation.

Table 47: AEs by High Level Term in the Infection and Infestations SOC Occurring in ≥1% of the Combined Vedolizumab Group (C13007)

	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
High-Level Term, n (%)	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA[b] N = 148	VDZ Q4W[c] (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Patients with at least 1 AE	64 (42)	69 (45)	71 (46)	57 (39)	219 (43)	121 (40)	359 (44)
Upper respiratory tract infections	29 (19)	35 (23)	43 (28)	27 (18)	106 (21)	56 (19)	184 (23)
Abdominal and gastrointestinal infections	11 (7)	10 (6)	13 (8)	7 (5)	39 (8)	18 (6)	62 (8)
Lower respiratory tract and lung infections	7 (5)	6 (4)	12 (8)	7 (5)	30 (6)	14 (5)	48 (6)
Urinary tract infections	5 (3)	8 (5)	6 (4)	5 (3)	28 (6)	10 (3)	42 (5)
Influenza viral infections	8 (5)	7 (5)	5 (3)	3 (2)	10 (2)	11 (4)	22 (3)
Herpes viral infections	5 (3)	1 (< 1)	5 (3)	4 (3)	14 (3)	9 (3)	20 (2)
Infections NEC	3 (2)	2 (1)	6 (4)	1 (< 1)	12 (2)	4 (1)	20 (2)
Bacterial infections NEC	3 (2)	2 (1)	4 (3)	2 (1)	10 (2)	5 (2)	16 (2)
Skin structures and soft tissue infections	2 (1)	4 (3)	3 (2)	4 (3)	8 (2)	6 (2)	15 (2)
Viral infections NEC	3 (2)	6 (4)	1 (< 1)	3 (2)	7 (1)	6 (2)	14 (2)
Fungal infections NEC	1 (< 1)	2 (1)	2 (1)	3 (2)	9 (2)	4 (1)	13 (2)
Candida infections	4 (3)	1 (< 1)	4 (3)	1 (< 1)	6 (1)	5 (2)	11 (1)
Dental and oral soft tissue infections	2 (1)	4 (3)	1 (< 1)	2 (1)	5 (< 1)	4 (1)	10 (1)
Ear infections	0	2 (1)	3 (2)	1 (< 1)	5 (< 1)	1 (< 1)	10 (1)

Source: Sponsor Submission, Integrated Summary of Safety, Table 4-51, pages 231 - 232

Serious infections occurred infrequently in all treatment groups with 54 patients (5%) reporting serious adverse events in the infections and infestations SOC (3% ITT placebo; 3% non-ITT placebo; 6% combined vedolizumab). The frequency of SAEs in the Infections and Infestations SOC was higher in the VDZ groups than the Placebo groups. Of the SAEs reported, only anal abscess, abdominal abscess, gastroenteritis, appendicitis, and device related infection were reported by more than one patient. These results are summarized in Table 48 below.

There were three serious sepsis-related events reported in patients receiving vedolizumab (in Study C13007):

- Bacterial sepsis: Patient C13007-27003-705 (a 24 year old male) was hospitalized for Gram (-) sepsis twelve days after his fourth dose of vedolizumab and was treated with antibiotics. The event resolved 10 days after onset, and was believed to be related to the study drug.
- Sepsis: Patient C13007-24001-705 (a 28 year old male) received five doses of vedolizumab and withdrew from the study approximately 6 weeks later initially for hospitalization for CD exacerbation and scleritis. Approximately 10 days later, the patient was transferred to the intensive care unit and had a central line inserted, and died 17 days later with reported cause of death of multiorgan dysfunction with consumptive coagulopathy, fungal sepsis, and CD with immunocompromised status. On CT scan, the patient was found to have a pneumoperitoneum. The event was believed to be related to the study drug.
- Septic shock: Patient C13007-24028-708 (a 30 year old male) was hospitalized for septic shock 28 days after his fourth dose of vedolizumab and died one day later. The event was believed to be related to the study drug.

Note that 1 serious event (device related sepsis) occurred in Patient C13007-27002-702 (a 34 year old male) in the non-ITT placebo group and resolved.

There were three serious lower respiratory infections reported in patients receiving vedolizumab (in Study C13007):

- Pneumonia (first patient): Patient C13007-19021-703 (a 40 year old female) was hospitalized for bronchopneumonia 9 days after her second dose of vedolizumab; the patient received antibiotics. The phlegm was not gram stained or cultured. The event resulted in discontinuation from the study 5 days later and was considered resolved another 4 days later. The event was believed to be related to the study drug.
- Pneumonia (second patient): Patient C13007-58154-701 (a 32 year old female) was hospitalized for community acquired pneumonia 22 days after her 12th dose of vedolizumab). The patient received antibiotics. The event was considered unresolved approximately 7 weeks later; the patient completed the study and continued into Study C13008. The event was considered related to the study drug.
- Lung infection: Patient C13007-07024-719 (a 58 year old male) presented to the emergency room 8 days after his fourth dose of vedolizumab with a serious pulmonary infection; a chest x-ray also revealed traumatic pneumothorax. The patient received antibiotics during hospitalization, and approximately 2 weeks later, the serious lung infection and traumatic pneumothorax were considered resolved. The lung infection was considered not related to the study drug.

Note that 1 patient in the non-ITT placebo group (Patient C13007-37005-703; a 75 year old male) experienced an SAE of bronchopneumonia 49 days after his eighth dose of placebo and died the same day.

There was one report of latent TB in Study C13007:

- Latent TB: Patient C13007-12013-703 (a 38 year old male from the Czech Republic) received 3 doses of vedolizumab over a 2-month period. One day after his last dose, the patient presented with a mild cough. A quantiferon test was positive; chest x-ray was negative (a quantiferon test had been negative prior to study enrollment). The event was reported as latent TB Quantiferon positive. The patient was afebrile, in good condition with normal physical findings and was administered isoniazid and pyridoxine. He was permanently discontinued from the study in response to the event. The event was reported as serious and the patient discontinued from the study. The event is considered unresolved. The event was considered related to the study drug.

Table 48: SAEs in the Infections and Infestations SOC reported by > 1 Patient (C13007)

	Maintenance ITT[a] (Responders to VDZ induction, randomized to Maint. Tmt. at Week 6)			Maintenance Non-ITT		Combined	
Preferred Term	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154	PLA[b] N = 148	VDZ Q4W[c] (Week 6 Nonresponders) N = 506	PLA N = 301	VDZ N = 814
Patients with at least 1 SAE	5 (3)	6 (4)	9 (6)	4 (3)	30 (6)	9 (3)	45 (6)
Anal abscess	0	1 (< 1)	2 (1)	1 (< 1)	13 (3)	1 (< 1)	16 (2)
Abdominal abscess	2 (1)	1 (< 1)	0	0	4 (< 1)	2 (< 1)	5 (< 1)
Gastroenteritis	1 (< 1)	1 (< 1)	0	0	1 (< 1)	1 (< 1)	2 (< 1)
Appendicitis	0	0	1 (< 1)	0	1 (< 1)	0	2 (< 1)
Device related infection	1 (< 1)	0	0	0	1 (< 1)	1 (< 1)	1 (< 1)

Source: Modified from Table 4-52 on Page 244 of the Integrated Summary of Safety

UC and CD Comparative Safety

A larger proportion of patients reported at least 1 infection in the combined vedolizumab group (43%) than the non-ITT placebo group (35%). The most commonly reported HLT were upper respiratory tract infections (17% non-ITT placebo; 24% combined vedolizumab), and this appears to have driven the difference in frequency of infections between groups. Other infection HLTs occurred with similar frequency between treatment arms. PTs in the infections and infestations SOC reported by ≥ 1% of patients in the combined vedolizumab group are summarized below.

Table 49: Infection AEs that occurred in ≥1% of patients in the combined VDZ group by PT

Preferred Term, n (%)	VDZ/PLA N = 279	PLA/PLA N = 297	VDZ/VDZ N = 1434
Pts with at least 1 AE	116 (42)	103 (35)	622 (43)
Nasopharyngitis	29 (10)	21 (7)	180 (13)
Upper Respiratory Tract Infection	19 (7)	19 (6)	106 (7)
Bronchitis	11 (4)	10 (3)	57 (4)
Influenza	10 (4)	5 (2)	51 (4)
Urinary Tract Infection	10 (4)	8 (3)	49 (3)
Sinusitis	10 (4)	3 (1)	44 (3)
Gastroenteritis	10 (4)	3 (1)	35 (2)
Anal Abscess	3 (1)	4 (1)	30 (2)
Pharyngitis	6 (2)	1 (<1)	24 (2)
Oral Herpes	6 (2)	4 (1)	20 (1)
Gastroenteritis, viral	2 (<1)	3 (1)	15 (1)

Source: Applicant Submission, Integrated Summary of Safety, Tables 18.2.2.2A and 18.2.2.16A

Serious infections occurred more frequently in CD patients in C13007 than in UC patients in C13006. In UC patients, serious infections were reported by 20 patients and at a similar frequency between dose groups (3% ITT placebo; 3% non-ITT placebo; 2% combined vedolizumab). In Study C13007, serious infections were reported in 5 (3%), 4 (3%), and 45 (6%) of patients in the VDZ/PLA, PLA/PLA, and VDZ/VDZ groups, respectively. Anal abscesses were the most frequently reported serious AE among CD patients, and the frequency was highest in the non-ITT vedolizumab group. In addition, there were 4 sepsis-related serious AEs in Study C13007, and 2 of these patients died (see CD Comparative Safety subsection above).

Systemic infections from enteric pathogens occurred in very small numbers, so comparisons are difficult to make. There were no cases of Listeria or Salmonella in C13006 or C13007; however, there were 6 cases of C. difficile and 2 cases of Campylobacter infections in patients who received vedolizumab, and 0 cases in patients who received placebo only. One case of C. difficile in a patient with CD was an SAE that resolved after 5 days, and one case was nonserious but led to study discontinuation. The remaining 4 cases were considered mild to moderate in severity and resolved. In addition, 1 patient from C13011 who received vedolizumab was diagnosed with Campylobacter infection and 1 with salmonella.

Fifty-one patients reported Herpes viral infections, however, none were serious, all were considered mild to moderate in intensity, and the majority were oral herpes. The rates of herpes infections were similar between treatment groups (3% ITT placebo, 2% non-ITT placebo, and 3% combined vedolizumab). Three herpes infections led to study discontinuation, 1 case of herpes zoster in an ITT-placebo patient from C13006, and 1 case each of herpes zoster and oral herpes in C13007.

A similar AE profile in the infections and infestations SOC was seen for patients with baseline concomitant use of immunomodulators and/or corticosteroids. As in the overall population, a larger proportion of patients in the combined vedolizumab group (43%) experienced at least 1 infectious AE, compared to 36% in the non-ITT placebo group. The most commonly reported AEs were similar in the subgroup of patients with baseline concomitant immunomodulators and/or corticosteroids and included nasopharyngitis, upper respiratory tract infection, bronchitis, and urinary tract infections.

Long-term Safety

The frequency of infections, including commonly reported infections (URI, gastrointestinal, UTI, influenza), fungal infections, and herpes infections did not increase with continued exposure to vedolizumab to 48 months. In addition to the information summarized above, there were 4 reports of tuberculosis among patients treated with vedolizumab which all occurred in the first 18 months of treatment. All were considered to be primary infections, and no extrapulmonary manifestations were reported.

Table 50: Serious Adverse Events in the Infections and Infestations SOC that Occurred in > 2 Patients Overall by Preferred Term and Indication

Preferred Term, n (%)	*Ulcerative Colitis N = 894*	*Crohn's Disease N = 1349*	*Total N = 2243*
Patients with at least 1 serious infection adverse event	42 (5)	113 (8)	155 (7)
Anal abscess	0	27 (2)	27 (1)
Gastroenteritis	3 (<1)	13 (<1)	16 (<1)
Pneumonia	7 (<1)	8 (<1)	15 (<1)
Abdominal abscess	0	10 (<1)	10 (<1)
Clostridium Difficile colitis	6 (<1)	4 (<1)	10 (<1)
Appendicitis	4 (<1)	5 (<1)	9 (<1)
Cellulitis	3 (<1)	3 (<1)	6 (<1)
Diverticulitis	1 (<1)	3 (<1)	4 (<1)
Pelvic abscess	1 (<1)	3 (<1)	4 (<1)
Perirectal abscess	0	4 (<1)	4 (<1)
Clostridial infection	1 (<1)	2 (<1)	3 (<1)
Cytomegalovirus colitis	2 (<1)	1 (<1)	3 (<1)
Gastroenteritis viral	0	3 (<1)	3 (<1)
Pulmonary tuberculosis	1 (<1)	2 (<1)	3 (<1)
Urinary tract infection	1 (<1)	2 (<1)	3 (<1)

Source: Sponsor Submission, C13008 Complete Study Report: 120-day safety update

Other notable serious infection AEs reported by ≤2 patients included salmonella, giardiasis, Klebsiella infection, Listeria meningitis, esophageal candidiasis, viral meningitis, and sepsis.

Reviewer comment: A higher proportion of patients in vedolizumab treated groups reported 1 or more infectious AE, than in the placebo groups. This appeared to be largely driven by a higher rate of infections involving the upper respiratory and nasopharyngeal tract, and these AEs were generally nonserious. SAEs of infection occurred infrequently and at a similar frequency in all of the treatment groups. Serious infections occurred more frequently in CD patients than in UC patients, and this appeared to be primarily driven by increased numbers of abscesses in the CD population. The number of infections from enteric pathogens was very small and difficult to compare, though there were more cases in the vedolizumab group than placebo. There was no observed increase in AE rates among the subgroup of patients on concomitant corticosteroids and/or immunomodulators.

Infusion related Events and Hypersensitivity reactions

Infusion-related events were analyzed as AEs assessed by the investigatory to be infusion-related and AEs that occurred within 1 calendar day of an infusion. Patients were to be monitored for infusion-related reactions during and after infusions and report the development of symptoms consistent with infusion-reactions (e.g. hives, pruritus) to the investigator. The ISS analyzed investigator-defined infusion related events. Adverse events defined by the investigator as infusion-related reactions were in the SOCs of general disorders and administration site conditions, skin and subcutaneous tissue disorders, immune system disorders, and respiratory, thoracic, and mediastinal disorders.

CD Comparative Safety

Investigator-defined infusion-related events were uncommon and were seen at similar rates in patients that received a dose of vedolizumab as patients receiving placebo in Study C13007 [39 (4%) of the 967 patients in the combined vedolizumab and ITT placebo groups vs. 8 (5%) of the 148 patients in the 5% non-ITT placebo group). One patient, described below, experienced an infusion-related reaction that was considered serious and resulted in discontinuation from the study, and an additional 5 vedolizumab-treated patients experienced reactions resulting in study dose interruption (a dose was considered interrupted if it was started, stopped, then re-started again and a complete dose was administered for the visit).

- Patient C13007-13006-703 (a 44 year old female from Denmark) experienced dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate 13 minutes after the start of her second vedolizumab infusion. The infusion was discontinued and the patient was treated with oxygen, an antihistamine, and IV hydrocortisone. The event was noted as resolved approximately 3 hours later. The patient was discontinued from the study due to the event. The SAE of infusion-related reaction was considered to be related to study drug

UC and CD Comparative Safety

Across the UC and CD phase 3 induction/maintenance studies, 3% of patients who received only placebo had an AE defined by the investigator as infusion-related, compared to 4% of patients who received at least 1 dose of vedolizumab (3% ITT placebo and 4% combined vedolizumab). Four patients, described below, discontinued from C13006 and C13007 due to an infusion-related reaction, and an additional 11 vedolizumab-treated patients experienced reactions that resulted in interruption of an infusion.

In addition to the 1 patient described above, 3 patients from C13006 described below experienced an infusion-related reaction resulting in discontinuation from the study.

- A 47-year-old female enrolled in C13006 reported right eye pruritis and swelling approximately 1 hour after completion of her first and only vedolizumab infusion. She was treated with loratadine and the event had resolved by 9 hours after completion of the infusion. The patient discontinued from the study due to this reaction.

- A 28-year old male enrolled in C13006 developed a pruritic, urticarial rash involving the arms, face, and flank approximately 10 minutes after his 6th dose of vedolizumab was

started. Hydrocortisone and promethazine were administered and the event resolved by 1 ½ hours after it started. The patient discontinued from the study due to this event.

- A 41-year old male enrolled in C13006 developed flushing, tongue thickening, tinnitus, pruritus, and erythema 26 minutes after initiation of his third dose of vedolizumab. The patient was treated with IV hydrocortisone and the event resolved 5 minutes after it started. The patient discontinued from the study due to this event.

Table 51 below summarizes investigator defined infusion-related events in this population.

Table 51: Summary of AEs Defined by the Investigator as Infusion-Related Reactions by SOC and HLT

System Organ Class, n (%) High-Level Term	VDZ/PLA N = 279	PLA/PLA N = 297	VDZ/VDZ N = 1434
Patients with at least 1 AE	**8 (3)**	**9 (3)**	**61 (4)**
General disorders and administration site conditions	5 (2)	4 (1)	16 (1)
Asthenic conditions	2 (<1)	2 (<1)	5 (<1)
Feelings and sensations NEC	0	0	4 (<1)
Infusion site reactions	2 (<1)	1 (<1)	3 (<1)
Febrile disorders	0	0	3 (<1)
Pain and discomfort NEC	1 (<1)	0	1 (<1)
General signs and symptoms NEC	0	0	1 (<1)
Product physical issues	0	0	1 (<1)
Edema NEC	0	1 (<1)	0
Skin and subcutaneous tissue disorders	0	0	14 (<1)
Pruritus NEC	0	0	6 (<1)
Rashes, eruptions and exanthems NEC	0	0	3 (<1)
Urticarias	0	0	3 (<1)
Dermatitis and eczema	0	0	2 (<1)
Erythemas	0	0	2 (<1)
Dermal and epidermal conditions NEC	0	0	1 (<1)
Purpura and related conditions	0	0	1 (<1)
Immune system disorders	0	0	1 (<1)
Allergic conditions NEC	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	1 (<1)	0	3 (<1)
Breathing abnormalities	0	0	1 (<1)
Coughing and associated symptoms	0	0	1 (<1)
Upper respiratory tract signs and symptoms	0	0	1 (<1)
Nasal congestion and inflammations	1 (<1)	0	0

Source: Sponsor Submission, Integrated Summary of Safety, page 335 (Table 4-79)

Of patients participating in Study C13008, 3% of UC patients and 4% of CD patients had an investigator defined infusion-related reaction (this includes reactions occurring across the qualifying study, where applicable).

Reviewer comments: Infusion-related reactions occurred infrequently and at a rate of approximately 4% in patients receiving vedolizumab. There was at least 1 case of anaphylaxis and multiple cases of urticaria. While the risk of infusion-related reactions appears to be less than other biologics, the potential should be included in the labeling.

Malignancies:

A total of 17 patients exposed to vedolizumab across the UC and CD clinical development program were diagnosed with malignancy, which were assessed by the investigator as serious. In addition, there were 4 cases of colonic dysplasia reported. This included 6 reported malignancies out of 1434 patients (0.4%) exposed to vedolizumab during the controlled clinical trials including one patient with basal cell and squamous cell carcinoma. An additional patient from C13006 who received only placebo was diagnosed with malignancy (0.3% of 297 total placebo patients from C13006 and C13007). The remainder of malignancies in patients exposed to vedolizumab occurred during long-term open-label treatment (C13008). There were no reports of malignancies in the Phase 1b and Phase 2 safety population or in Study C13011. **Table 52**Table 52 below provides a summary of vedolizumab-treated patients with serious malignancies.

Table 52: Summary of Malignancies[1]

Study/Patient ID	Age/ Gender/ Race	Malignancy (Preferred Term)	Number of VDZ infusions/ Days after last infusion	Assessment of relatedness by investigator/ FDA reviewer
UC Patients				
C13006: C13006-37005-605	73.7/M/W	Colon cancer	2/30	No/No
C13006: C13006-53003-691	32.7/M/ W	Colon cancer	7/71	Yes/No
C13006: C13006-58132-603	40.5/M/W	Transition cell carcinoma	2/314	No/No
C13008: C13006-03003-604	47.4/M/W	Malignant melanoma	2/8	No/No
C13008: C13006-04006-647	44.1/M/W	Colon cancer with metastases to peritoneum	8/69	Yes/No
C13008: C13006-07113-603	50.4/M/W	Renal cancer	29/13	Yes/Possibly
C13008: C13006-58104-609	70.2/M/W	Malignant melanoma	9/13	No/No
C13008: C13006-58141-807	75.3/F/W	Malignant lung neoplasm	4/94	No/No
Crohns disease				
C13007: C13007-07024-706	20.7/F/W	Carcinoid tumor of the appendix	13/20	No/No
C13007: C13007-18005-709	45.2/F/W	Breast cancer	2/1	No/No
C13007: C13007-58115-703	52.1/F/W	Squamous cell carcinoma (skin)	10/	No/No
C13008: C13007-12013-702	51.1/F/W	Malignant hepatic neoplasm	41/25	Yes/Possibly
C13008: C13007-19004-708	42.9/M/W	B-cell lymphoma	21/97	No/No
C13008: C13007-42009-703	49.7/M/W	Squamous cell carcinoma (skin)	37/20	Yes/Possibly
C13008: C13007-07032-806	69.0/F/W	Hepatic neoplasm malignant/ Lung cancer malignant	3/15	No/No
C13008: C13011-07015-901	45.5/F/W	Colon cancer	8/16	Yes/No
C13008: C13011-58012-902	46.8/M/W	Basal cell carcinoma	12/18	Yes/Possibly

Source: Sponsor Submission, Integrated Summary of Safety Page 292 and 120-day Safety Updated Pages 48-49
[1] This summary includes malignancies reported as serious by the investigator

The overall incidence rate for colon cancer was 0.66 per 1000 person-years. This is lower than the incidence rate of 2.07 per 1000 person-years found in patients with moderate to severe IBD in the HIRD database.

Reviewer Comments: The overall number of malignancies was low and no malignancy type predominated. Nonclinical data did not suggest carcinogenic potential with vedolizumab (see nonclinical review). In controlled trials, the proportion of patients with malignancies was similar across treatment groups; however, comparisons are difficult to make given the low number of malignancies and limited long-term exposure. The rates

of colon cancer appear to be consistent with what is expected in this patient population, based on the HIRD database.

Neurologic-related Events

CD Comparative Safety

In Study C13007, 30% of patients in the ITT-placebo arm reported at least 1 nervous system event, compared to 20% and 22% in the non-ITT placebo and combination vedolizumab arms, respectively. In Study C13007, paresthesias and dysesthesias were observed in 2.79 % of 718 vedolizumab treated patients in study C13007 and there were no reports in 148 placebo treated patients. However, in C13006, paresthesias and dysesthesias were approximately equally distributed between the vedolizumab and placebo arms (1.2 % and 1.3 %, respectively) (see UC Comparative Safety subsection below).

UC Comparative Safety

The results were similar in the Phase 3 UC Study (C13006). A similar proportion of patients reported at least 1 nervous system event in each treatment arm with 28 (19%) of placebo patients and 129 (21%) of combined vedolizumab treated patients reporting at least one neurological AE. The rates were similar in the patients who received vedolizumab during induction and placebo during the maintenance phase (18% placebo-ITT). The most frequently reported HLT was Headaches NEC which was reported at similar rates in the combined vedolizumab and ITT-placebo group and less frequently in the non-ITT placebo group (13% ITT placebo; 10% non-ITT placebo, 14% combined vedolizumab). The next most common HLT reported was Neurological signs and symptoms NEC, which was reported at similar rates across groups (2% ITT placebo; 1% non-ITT placebo, 4% combined vedolizumab). No patient discontinued from Study C13006 due to a nervous system event, and only one event was designated as serious by the investigator (syncope by patient in ITT VDZ Q4W group).

Long-term UC and CD Safety

In the long-term safety study, C13008, 30% of patients reported at least 1 nervous system AE as of June 27, 2013, with headaches reported most commonly in UC and CD patients. Nervous system AEs were reported with similar frequencies for UC and CD patients. Nervous system AEs reported by greater than 1% of patients are summarized by indication in Table 53, below.

Table 53: Nervous System AEs in Long-term Safety Group

High Level Term, n (%)	Ulcerative Colitis N = 894	Crohn's Disease N = 1349	Total N = 2243[a]
Patients with at least 1 nervous system AE	242 (27)	437 (32)	679 (30)
Headaches NEC	141 (16)	266 (20)	411 (18)
Neurological signs and symptoms NEC	41 (5)	101(7)	147 (7)
Sensory abnormalities NEC	32 (4)	51 (4)	85 (4)
Paresthesias and dysesthesias	21 (2)	31 (2)	73 (3)
Migraine headaches	19 (2)	27 (2)	51 (2)

Source: Sponsor Submission, Integrated Summary of Safety, 120-day Safety Update, Table 4-21

[a] For patients in C13008 who received vedolizumab in qualifying studies and rolled into C13008, the frequency of AEs was analyzed across the originating study and Study C13008. For patients who received placebo during the previous study, AEs were not counted during the time of placebo administration.

Reviewer comment: Neurologic AEs were generally reported at similar rates with vedolizumab (21% C13006; 22% C13007) and placebo (19% C13006; 20% C13007) in Phase 3 controlled trials. The exception was paresthesias and dysesthesias which were reported at a higher frequency in vedolizumab treated patients than placebo treated patients in Study C13007. This difference was not seen in C13006 (paresthesias and dysesthesias were reported in 2-3% of patients with long-term treatment). The lack of such a reporting difference in UC patients during controlled trials is difficult to explain, and it is possible the difference in CD patients is related to underlying disease or chance. Continued monitoring for drug-induced neuropathies in the postmarketing setting may be warranted. The most frequently reported neurologic AEs were headache and dizziness. (See also Section 7.7 of this review.)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events in C13006 and C13007 were nasopharyngitis, headache, arthralgia, Crohn's disease, pyrexia, abdominal pain, upper respiratory tract infection, and ulcerative colitis. The rates of common adverse events were similar between the combined vedolizumab group and the non-ITT placebo group. The frequency of AEs occurring in at least 5% of patients in the combined vedolizumab group are summarized in Table 54 below.

Table 54: Common AEs in CD and UC - Induction and Maintenance (Studies C13006 and C13007)

Preferred Term, n (%)	VDZ/PLA Patients n (%) N = 279	PLA/PLA Patients n (%) N = 297	VDZ/VDZ Patients n (%) N = 1434
Patients with at least 1 AE/Total Number of events	234 (84)	232 (78)	1203 (84)
Nasopharyngitis	29 (10)	21 (7)	180 (13)
Headache	43 (15)	32 (11)	177 (12)
Arthralgia	36 (13)	29 (10)	166 (12)
Crohn's Disease	29 (10)	36 (12)	164 (11)
Nausea	26 (9)	23 (8)	128 (9)
Pyrexia	30 (11)	22 (7)	127 (9)
Abdominal Pain	20 (7)	29 (10)	114 (8)
Upper respiratory tract infection	19 (7)	19 (6)	106 (7)
Colitis ulcerative	29 (10)	29 (10)	97 (7)
Fatigue	14 (5)	10 (3)	86 (6)
Vomiting	14 (5)	16 (5)	75 (5)
Anemia	10 (4)	20 (7)	70 (5)
Cough	10 (4)	10 (3)	70 (5)

Source: Sponsor Submission Integrated Summary of Safety, pages 167-168

The frequency of AEs considered severe was also similar between the 3 treatment groups in Studies C13006 and C13007. Thirteen percent of patients in the ITT placebo reported severe AEs, compared to 14% in the non-ITT placebo and 15% in the combined vedolizumab group. Crohn's disease, abdominal pain, and ulcerative colitis were the only AEs categorized as severe which were reported in at least 1% of the combined vedolizumab group, and these occurred at similar frequencies in the 3 treatment groups.

Reviewer comment: In both the UC and CD populations,infections involving the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection) were the most commonly reported infection and occurred with greater frequency in vedolizumab treated patients than placebo. Oronasal-associated lymphocytes show primary α4β7 expression, suggesting the MAdCAM-1 interactions have a role in nasal infections. The greater frequency of upper respiratory tract infections is consistent with vedolizumab's mechanism of action in inhibiting the α4β7-MAdCAM-1 interaction, and there was no increase in serious infection related adverse events seen. There is the potential that this represents an off target event, however, and this should continue to be monitored in the post-marketing setting. Furthermore, including language that vedolizumab is (b) (4) *may be misleading and this reviewer believes should be omitted.*

7.4.2 Laboratory Findings

Combined UC and CD Population:

In both the UC and CD Induction/Maintenance Safety Populations, there were no clinically important treatment group differences in the proportion of patients who had shifts from baseline to on-study laboratory values. The most common marked laboratory abnormality in Studies C13006 and C13007 was absolute lymphocyte counts < 0.5 x 10^9/L, which was observed in approximately 5% of patients who received vedolizumab. This lab abnormality was also

observed in 4% of patients who received placebo only. No patients in Studies C13006 or C13007 met the laboratory criteria for Hy's law laboratory criteria for drug-induced liver injury (ALT ≥3 x ULN and bilirubin ≥ 2 x ULN at the same visit).

Table 55: Summary of Marked Abnormalities[1] in Clinical Lab Values for the Combined Safety Population (C13006 and C13007)

Analyte, n (%)	VDZ/PLA N = 279	PLA/PLA N = 297	VDZ/VDZ N = 1434
Hemoglobin ≤ 70 g/L	1 (<1)	3 (<1)	20 (1)
Lymphocytes < 0.5 x 10^9/L (absolute count)	10 (4)	18 (6)	70 (5)
Leukocytes < 2.0 x 10^9/L (absolute value)	1 (<1)	2 (<1)	4 (<1)
Platelets <75.0 x 10^9/L	2 (<1)	1 (<1)	0
Neutrophils < 1.0 x 10^9/L (absolute count)	4 (1)	3 (1)	6 (<1)
Prothrombin time > 1.25 x ULN	10 (4)	12 (4)	59 (4)
ALT > 3.0 x ULN	6 (2)	3 (1)	22 (2)
AST > 3.0 x ULN	7 (3)	0	16 (1)
Bilirubin > 2.0 x ULN	2 (<1)	2 (<1)	7 (<1)
Amylase > 2.0 x ULN	3 (1)	8 (3)	20 (1)
Lipase > 2.0 x ULN	3 (1)	8 (3)	28 (2)

Source: Sponsor Submission, Integrated Summary of Safety, Table 18.2.3.1

[1] Marked abnormalities were outside the pre-defined criteria for marked abnormality and had an on-treatment value more extreme than the baseline value

Reviewer Comments: Changes in laboratory findings was infrequent and mostly similar between treatment groups with exceptions noted in the section on Off-Target Effects (see Section 7.7).

7.4.3 Vital Signs

No clinically important treatment differences in the mean change in vital signs were observed between-groups in the UC and CD Induction/Maintenance Safety Population.

7.4.4 Electrocardiograms (ECGs)

In Study C13007, a total of 5 patients (1 ITT placebo and 4 vedolizumab) had a clinically significant ECG abnormality. None of these ECG abnormalities led to premature discontinuation from study. An additional 5 patients had clinically significant ECG findings during the long-term safety study, C13008. Two UC patients and 3 CD patients had abnormal ECG findings, four of which were assessed by the study investigator as not related to study drug. One ECG finding of coronary sinus rhythm, incomplete right bundle branch block in a 20-year-old patient with CD was reported as mild and related to vedolizumab. A repeat ECG 1 month later was within normal limits.

Reviewer Comments: There does not appear to be an increase in ECG abnormalities in vedolizumab treated patients.

See also discussion of Study C13009 in Section 7.4.5.

7.4.5 Special Safety Studies/Clinical Trials

Study C13009:

The effect of vedolizumab on cardiac repolarization was evaluated in Study C13009. A total of 87 subjects were enrolled in the study. In Part 1 (unblinded), 13 subjects were assigned to a single IV dose of 300-mg Process C vedolizumab. In Part 2 (blinded, randomized), 23 subjects were randomized to a single IV dose of 600-mg Process B vedolizumab, 26 subjects were randomized to a single IV dose of 600-mg Process C vedolizumab, and 25 subjects were randomized to a single IV dose of placebo.

Overall, there were no marked mean changes in ECG parameters. Two (8%) subjects in the placebo treatment group and 10 (20%) subjects in the vedolizumab treatment group had maximum post baseline QTcF values between 430 to 449 msec, and 7 (14%) subjects in the vedolizumab treatment group had maximum post baseline QTcB values between 430 to 449 msec. Four (17%) subjects in the placebo treatment group and 4 (9%) subjects in the vedolizumab treatment group had a ≥ 30 msec change in QTcB, and 2 (4%) subjects in the vedolizumab treatment group had a ≥ 30 msec change in QTcF. No subjects had QTc > 450 msec or had ≥ 60 msec change in QTc from baseline.

One (5%) subject in the placebo treatment group had an abnormal ECG on Day 85 that was considered clinically significant. The abnormality was reported as a single, mild, drug-related cardiac AE of atrial fibrillation; no action was taken and the event resolved. No subjects in the vedolizumab treatment groups had abnormal ECG parameters during the study that were considered clinically significant.

Study C13012:

Study C13012 was a phase 1 single-arm study in healthy adults to assess the effects of a single 450mg intravenous dose of vedolizumab on the CD4+:CD8+ lymphocyte ratio in the CSF of humans. One hypothesis on the etiology for the increased risk of PML with natalizumab is that it prevents the ingress of leukocytes into the CNS. Vedolizumab did not affect CD4+ counts, CD8+ counts, or the CD4+:CD8+ lymphocyte ratio in the CSF of the subjects studied. The applicant suggests that this supports that vedolizumab is unlikely to lead to impairment of the CNS immune system and potentially increased PML risk.

No special safety studies were performed in the vedolizumab clinical development program. The RAMP algorithm was developed to mitigate the risk of PML and identify early any potential PML cases. This is described in detail in sections 7.2.6 and 7.3.5.

7.4.6 Immunogenicity

The immunogenicity of vedolizumab was assessed across multiple studies and the effects of human antihuman antibodies (HAHA) on safety were evaluated. A validated ELISA immunoassay with a sensitivity of 440 pg/mL was used to determine the presence of HAHA. Immunogenicity assessment consisted of an initial screening using dilutions of 1:5 and 1:50; positive samples were subsequently confirmed positive, tittered, and tested for neutralization. Patients were considered to be transiently positive if they had at least one positive HAHA sample and no consecutive HAHA positive samples, while patients categorized as persistently positive had 2 or more consecutive positive samples. To better characterize the overall

immunogenicity rate in vedolizumab exposed patients, immunogenicity assessments were performed at 5 half-lives (16 weeks) after the final dose.

In Studies C13006 and C13007, patients were tested for HAHA and neutralizing HAHA against vedolizumab at Weeks 0 (predose), 6, 14, 26, 38, 52 (or Early Termination), and 66 (Safety Visit).

In the group of patients who received continuous vedolizumab in the induction and maintenance phases of C13006 and C13007, 56 of 1434 (4%) were HAHA-positive at any time. Of these patients, 9 were persistently positive, and 33 developed neutralizing antibodies. The overall rate of HAHA-positive off drug (defined as 5 half lives or 16 weeks after last dose) was 10% (32 out of 320 patients). Co-administration with immunosuppressants appeared to decrease the overall HAHA rate and the rate of persistent HAHA and neutralizing antibodies. This was particularly evident in the ITT-placebo group (n = 279) where only 1 (3%) patient who received concomitant immunomodulator therapy was HAHA-positive, compared to 30 (12%) patients who did not receive concomitant therapy.

Three of 61 (5%) combined vedolizumab patients who had an infusion-related reaction were persistently HAHA positive, while 6 of 1320 (<1%) who did not have an infusion reaction were persistently positive. See Table 56 below.

Table 56: Summary of AE Defined by Investigator as Infusion-Related Reactions by HAHA status

AEs Defined by Investigator as Infusion-Related Reactions (Yes/No)	ITT			Non-ITT		Combined
	Placebo N = 279	VDZ Q8W N = 276	VDZ Q4W N = 279	Placebo N = 297	VDZ Q4W N = 879	VDZ N = 1434
Yes, n (%)						
HAHA-negative	7 (88)	11 (92)	18 (100)	9 (100)	29 (94)	58 (95)
HAHA-positive	1 (13)	1 (8)	0	0	2 (6)	3 (5)
Transiently positive	0	0	0	0	0	0
Persistently positive	1 (13)	1 (8)	0	0	2 (6)	3 (5)
Any Neutralizing HAHA-positive	0	0	0	0	2 (6)	2 (3)
No, n (%)						
HAHA-negative	227 (84)	257 (97)	258 (99)	279 (97)	805 (95)	1320 (96)
HAHA-positive	44 (16)	7 (3)	3 (1)	8 (3)	43 (5)	53 (4)
Transiently positive	14 (5)	6 (2)	3 (1)	3 (1)	38 (4)	47 (3)
Persistently positive	30 (11)	1 (<1)	0	5 (2)	5 (<1)	6 (<1)
Any Neutralizing HAHA-positive	24 (9)	4 (2)	3 (1)	4 (1)	24 (3)	31 (2)

Source: Sponsor Submission, Summary of Clinical Pharmacology 2.7.2, Table 6-3
Transiently positive: all patients who have at least one positive HAHA sample and no consecutive HAHA-positive samples
Persistently positive: all patients who have 2 or more consecutive positive HAHA samples

Reviewer comments: The presence of HAHA may slightly increase the risk of infusion reactions, however, the small number of HAHA positive patients as well as the small number of infusion reactions preclude any definitive conclusions. There are limitations in the assessment of immunogenicity. For example, the observed incidence of HAHA may be an underestimation due to drug interference in the assay and can also be influenced by sample handling, timing of sample collection, concomitant medications, and underlying disease.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See individual adverse event sections described elsewhere. No dose dependent AEs were noted.

7.5.2 Time Dependency for Adverse Events

When looking at AE rates by duration of vedolizumab exposure in Study C13008, no increased frequency of AEs were seen with longer periods of use, nor were any time dependent AEs identified. See Table 44 for a summary of serious adverse events by months of drug exposure.

7.5.3 Drug-Demographic Interactions

UC and CD Comparative Safety

The applicant analyzed the safety datasets by age, race, sex, body weight, baseline disease activity, and creatinine clearance in the UC and CD combined safety populations. The information below includes combined data from the induction and maintenance phases of Studies C13006 and C13007, as these studies included 52 weeks of treatment with placebo comparison and combining the data increased the power for subgroup analyses.

There were insufficient patients ≥ 65 years of age (< 3% of the UC and CD Maintenance Safety Population) to allow meaningful comparisons between age groups, however, frequently reported AEs were similar. In the 34 patients ≥ 65 years of age from the combined vedolizumab group, arthralgia and headache were reported most commonly, and of these, only arthralgia was reported more commonly in the combined vedolizumab group compared to placebo (n = 8 (24%) vs n = 4 (18%), respectively). Similarly, meaningful treatment group comparisons within race subgroups was unfeasible, given the low number of patients who were identified as Asian, Black, and Other races, making.

Analysis of safety by sex did not show any clear increased risk for AEs by sex with vedolizumab treatment. Headaches, arthralgia, Crohn's disease were reported more frequently in females than in males (≥ 3% difference) in the combined vedolizumab group, but were also reported more frequently in females than males in the non-ITT placebo population. Adverse events reported by ≥ 10% of males or females in any treatment group were similar and are summarized in Table 57 below. No signal of increased risk for an adverse event or type of adverse event was observed when assessing AEs by weight or disease activity, and there were insufficient patients with creatinine clearance < 60 for meaningful comparisons.

Table 57: Adverse Events Reported by ≥ 10% of males or females in any treatment group, summarized by sex

	Female			Male		
Preferred Term, n (%)	VDZ/PLA	PLA/PLA	VDZ/VDZ	VDZ/PLA	PLA/PLA	VDZ/VDZ

	N = 138	N = 136	N = 691	N = 141	N = 161	N = 743
Patients with at least 1 AE	115 (83)	117 (86)	613 (89)	119 (84)	115 (71)	590 (79)
Nasopharyngitis	16 (12)	10 (7)	84 (12)	13 (9)	11 (7)	96 (13)
Headache	28 (20)	21 (15)	105 (15)	15 (11)	11 (7)	72 (10)
Arthralgia	18 (13)	21 (15)	92 (13)	18 (13)	8 (5)	74 (10)
Crohn's Disease	18 (13)	27 (20)	96 (14)	11 (8)	9 (6)	68 (9)
Nausea	19 (14)	14 (10)	86 (12)	7 (5)	9 (6)	42 (6)
Pyrexia	20 (14)	14 (10)	64 (9)	10 (7)	8 (5)	63 (8)
Abdominal pain	13 (9)	18 (13)	65 (9)	7 (5)	11 (7)	49 (7)
Upper respiratory tract infection	9 (7)	12 (9)	64 (9)	10 (7)	7 (4)	42 (6)
Ulcerative colitis	12 (9)	15 (11)	43(6)	17 (12)	14 (9)	54 (7)

Source: Sponsor Submission, Integrated Summary of Safety, page 404 Table 7-8

The applicant also analyzed the safety datasets by patient geographic region, prior TNFα antagonist use, and baseline concomitant immunomodulator and corticosteroid use. Patients were categorized by the following geographic region: North America, Western/Northern Europe, Africa/Asia/Australia, and Central Europe. Slight differences were noted in the frequency of AEs among patients in the combined vedolizumab group across geographic region, however the rates of AEs in the placebo group by geographic region were similar (Africa/Asia/Australia 82% VDZ, 82% PLA; Central Europe 73% VDZ, 71% PLA; North America 88% VDZ, 84% PLA; and Central Europe 91% VDZ, 92% PLA). No clinically significant difference in the frequency of commonly reported AEs was seen among the ITT placebo, non-ITT placebo, and combined vedolizumab groups.

A larger proportion of patients with a history of TNFα antagonist use reported a AEs, than patients without a history of use. However, rates of AEs were similar between treatment groups when assessed by history of previous TNFα antagonist use. Adverse events reported by ≥ 10% of patients in any treatment group by history of previous TNFα antagonist use are summarized below. Rates of serious adverse events were similar in the subgroup of patients with previous use, compared to the general population. See section 7.3.2 for additional information on serious adverse events in this subpopulation.

Table 58: Adverse Events Reported by ≥ 10% of patients in any treatment group, summarized by prior TNFα Use

	No Prior TNFα Use			Prior TNFα Use		
Preferred Term, n (%)	VDZ/PLA N = 150	PLA/PLA N = 152	VDZ/VDZ N = 588	VDZ/PLA N = 129	PLA/PLA N = 145	VDZ/VDZ N = 846
Patients with at least 1 AE	118 (79)	115 (76)	451 (77)	116 (90)	117 (81)	752 (89)
Nasopharyngitis	12 (8)	9 (6)	54 (9)	17 (13)	12 (8)	126 (15)
Headache	17 (11)	12 (8)	63 (11)	26 (20)	20 (14)	114 (13)
Arthralgia	11 (7)	12 (8)	50 (9)	25 (19)	17 (12)	116 (14)
Crohn's Disease	12 (9)	7 (5)	40 (7)	17 (13)	29 (20)	124 (15)
Nausea	11 (7)	10 (7)	28 (5)	15 (12)	13 (9)	100 (12)
Pyrexia	13 (9)	10 (7)	39 (7)	17 (13)	12 (8)	88 (10)
Abdominal pain	7 (5)	13 (9)	46 (8)	13 (10)	16 (110	68 (9)
Upper respiratory tract infection	6 (4)	9 (6)	41 (7)	13 (10)	10 (7)	65 (8)
Ulcerative colitis	19 (13)	16 (11)	36 (6)	10 (8)	13 (9)	61 (7)

Source: Sponsor Submission, Integrated Summary of Safety, page 415 - 416

Adverse events reported by ≥ 10% of patients in any treatment group were the similar when assessed by baseline immunomodulator and/or corticosteroid use and included nasopharyngitis, headache, crohn's disease, arthralgia, abdominal pain, upper respiratory tract infection, pyrexia, and ulcerative colitis. There were no significant differences in commonly

reported AEs among treatment group, nor was a signal of increased risk for an adverse event observed when assessing AEs by baseline concomitant drug use. See section 7.3.2 for additional information on serious adverse events in this subgroup of patients.

Reviewer Comment: This reviewer saw no apparent signals for increased risk for an adverse event or any type of adverse event when assessing AEs by a variety of demographic factors, including age, sex, geographic region, and prior treatments. While there appeared to be an increased proportion of AEs in patients with previous TNFα use, the rates of AEs were similar between treatment groups in this subset, suggesting patients with previous TNFα use may have more serious underlying disease and higher baseline risk for adverse events.

7.5.4 Drug-Disease Interactions

The safety evaluation included an evaluation controlling for baseline disease severity. There were insufficient patients with creatinine clearance < 60 mL/min to allow meaningful comparison.

There is the potential that disease improvement can impact CYP450 and thus lead to disease-drug-drug interactions. This was not thoroughly explored in the clinical development program and may be considered in a PMC. *See the Clinical Pharmacology review for additional information.*

7.5.5 Drug-Drug Interactions

Monoclonal antibody-drug interactions are not common and when they occur are likely from overlaps in the mechanism of action, alteration in target, or drug-disease interaction. In addition, monoclonal antibodies that modulate cytokine production may affect the regulation pathways of P450 enzymes. Vedolizumab was not found to modulate cytokine production in in vitro and clinical studies.

No adverse events were observed that were assessed as related to drug-drug interactions.

Reviewer comment: The risk of drug-drug interactions is low with vedolizumab, given it is an antibody and interacts only with integrin receptors. Nothing was observed during the clinical development program. See the clinical pharmacology review for additional information on drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See section 7.3.5 Submission Specific Primary Safety Concern

7.6.2 Human Reproduction and Pregnancy Data

No evidence of fetal harm from vedolizumab was found in nonclinical reproduction studies in New Zealand white rabbits and Cynomolgus monkeys, at doses up to 25 times the human dose. No adequate and well controlled studies of vedolizumab were performed in pregnant women.

Reviewer comment: the applicant proposes Pregnancy Category B based on the nonclinical data and lack of clinical data supporting vedolizumab's safety in pregnant women. This is appropriate. Lactation studies should be performed as a postmarketing requirement.

7.6.3 Pediatrics and Assessment of Effects on Growth

This drug has not yet been studied in children. The applicant has requested a Waiver of Pediatric Study for pediatric patients from birth to (b) (4) and a Deferral of Pediatric Study for pediatric patients (b) (4) to < 18.

Reviewer comment: The applicants waiver and deferral request appear appropriate to this reviewer. We generally have waived requirements for pediatric studies of CD treatments in children under the age of 6 years due to the low CD incidence in that age group; however, inclusion of patients as young as (b) (4) of age in the applicant's pediatric plan is acceptable. The final determination of waiver and deferral will be made upon presentation to the Pediatric Research Committee (PeRC) in January.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdosage reported in the vedolizumab clinical development program. Doses up to 10 mg/kg (approximately 2.5 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity.

7.7 Additional Submissions / Safety Issues

Evidence for off-target effects of vedolizumab

The applicant states that vedolizumab is a "gut-specific[34]" integrin antagonist that has a different mechanism of action (MOA) than natalizumab, and is, therefore, safer than natalizumab. Briefly, the applicant argues that vedolizumab blocks only lymphocyte receptor α4β7 and that MadCAM1 and fibronectin are the only counter-receptors for α4β7 (relevant references are in Table 59). Because MadCAM1, according to the applicant, is a gut-specific cell adhesion molecule, vedolizumab only acts on the gut, and is therefore also gut-specific. In contrast, natalizumab, an α4β1 antagonist, induces mobilization of bone marrow cells (Bonig et al. 2008) and leads to leukocytosis (Miller et al. 2003). Furthermore, natalizumab affects the adaptive immune response to extra-gastrointestinal challenges and inhibits leukocyte infiltration into the CNS (see references for Table 59). A decreased immune surveillance of the CNS together with mobilization of JC-infected[35] bone marrow cells have been postulated to be etiologic or contributing factors for the emergence of PML (progressive multifocal encephalopathy). The applicant states that none of these effects have been described with vedolizumab[36]. See Table 59.

Table 59 Vedolizumab vs. natalizumab - differences according to applicant

Physiologic Differences Between Vedolizumab and Natalizumab That are Relevant to the Development of PML

Pharmacologic Difference	Vedolizumab ($\alpha_4\beta_7$)	Natalizumab ($\alpha_4\beta_1$ and $\alpha_4\beta_7$)	Relevance to Events Leading to PML
1. Mobilization of cells from the bone marrow	No effect detected[5]	Induces[30, 31, 32]	Emergence of neurotropic JCV
2. Leukocytic infiltration of the CNS	No effect detected[22]	Inhibits[22]	Neutralization of JCV in the oligodendroglia
3. Broad sequestration of leukocytes in the vasculature	No effect detected[17, 22]	Induces leukocytosis[17, 22]	Pleiotropic impairment of immune surveillance
4. Adaptive immune response to extra-gastrointestinal challenges	No effect detected[28]	Inhibits[33]	Pleiotropic impairment of immune surveillance

CNS = central nervous system; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.

References:

5. Final Clinical Study Report C13009: A phase 1 single dose study to determine the pharmacokinetics, pharmacodynamics, safety, and tolerability of a lyophilized formulation (Process C drug product) of MLN0002 in healthy subjects. Cambridge (MA, USA): Millennium Pharmaceuticals, Inc.; 2010. Report C13009 CSR.

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22. Fedyk E. Evaluation of humanized monoclonal antibodies against alpha 4 integrins in the rhMOG-

[34] Sometimes the term "gut-selective" is used instead
[35] JC virus or John Cunningham virus (JCV) is the etiologic agent for PML
[36] Takeda: INTERDISCIPLINARY STUDY REPORT AMENDMENT p. 9

induced experimental autoimmune encephalomyelitis model in rhesus monkeys (Macaca mulatta). Cambridge (MA, USA): Millennium Pharmaceuticals, Inc; 2011. Report RPT-01673, Amendment 1.
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30. Bonig H et al. Increased numbers of circulating hematopoietic stem/progenitor cells are chronically maintained in patients treated with the CD49d blocking antibody natalizumab. Blood. 2008;111(7):3439-41.
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Adapted from: Takeda: INTERDISCIPLINARY STUDY REPORT AMENDMENT p. 38

An exploratory analysis of data from the Crohn's disease trial C13007 and the Ulcerative Colitis trial C13006 casts considerable doubt on the "gut-specificity" of vedolizumab. The exposition is followed by some possible mechanistic explanations and suggestions for labeling and postmarketing studies.

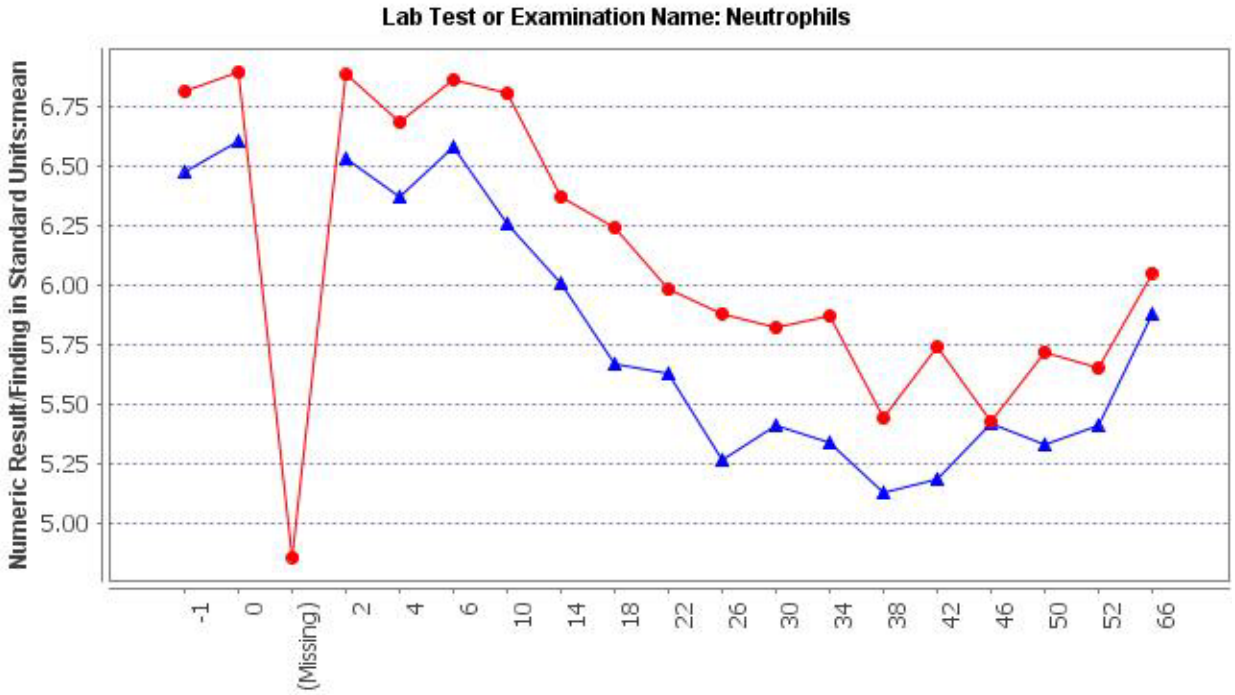
Probably no bone marrow effects

The applicant states that vedolizumab sequesters approximately 1% of leukocytes and natalizumab 40 %[37]. The sequestration of lymphocytes that have lost their home in the lymphoid tissues of the gut are part of the mechanism of action of vedolizumab and lymphocytosis that contributes minimally to the total white cell count (leukocytes) is expected and were indeed observed in study C13007 (data not shown). If the effect is limited to the gut homing lymphocytes, no increased numbers of cells of myeloid lineage (for example, neutrophils) are expected, neither mature granulocytes nor immature precursor cells such as myelocytes.

The following graph shows total neutrophil counts (as measured by automated cell counters) for the induction and maintenance phase of study C13007 in JReview.

[37] Takeda: INTERDISCIPLINARY STUDY REPORT AMENDMENT p. 38

Figure 19 Total neutrophil counts (average at each time point) for the induction and maintenance phase of study C13007 - JReview output



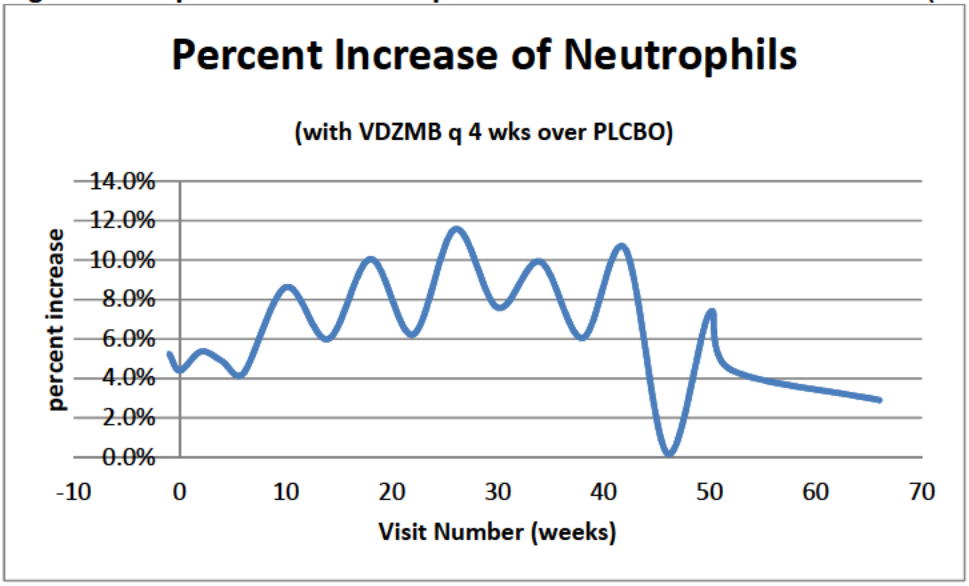
The graph shows that at every study visit the average number of neutrophils in the vedolizumab (q 4 weeks) arm is numerically higher than in the placebo arm with a possible normalization after completion of the study following visit 52 (52 weeks). Numerically, the following is seen (see Table 60):[38]

[38] It is not clear why there is a difference of neutrophils upon entry, prior to the use of vedolizumab. However, it is not likely that the neutrophil count of a randomly selected group of patients with the same disease should, even if there was a difference at the start of the study, remain elevated throughout the entire study period. The presence of increased myelocytes in the vedolizumab group further supports the conclusion that vedolizumab may have an effect on the bone marrow. The fluctuating course of the neutrophil increases is consistent with repeated dosing at intervals but other explanations are possible including a baseline difference that persisted.

Table 60 Neutrophil counts (average at each time point), difference, and percent change with vedolizumab Q4W vs. Placebo (C13007)

Visit Number	PLCBO	VDZMB	Difference	Percent Change
-1	6.47	6.81	0.34	5.3%
0	6.6	6.89	0.29	4.4%
2	6.53	6.88	0.35	5.4%
4	6.37	6.68	0.31	4.9%
6	6.58	6.86	0.28	4.3%
10	6.26	6.8	0.54	8.6%
14	6.01	6.37	0.36	6.0%
18	5.67	6.24	0.57	10.1%
22	5.63	5.98	0.35	6.2%
26	5.27	5.88	0.61	11.6%
30	5.41	5.82	0.41	7.6%
34	5.34	5.87	0.53	9.9%
38	5.13	5.44	0.31	6.0%
42	5.19	5.74	0.55	10.6%
46	5.42	5.43	0.01	0.2%
50	5.33	5.72	0.39	7.3%
52	5.41	5.65	0.24	4.4%
66	5.88	6.05	0.17	2.9%
Average increase over placebo				6.4%

Figure 20 Graph of relative neutrophil increases seen with vedolizumab* (C13007)

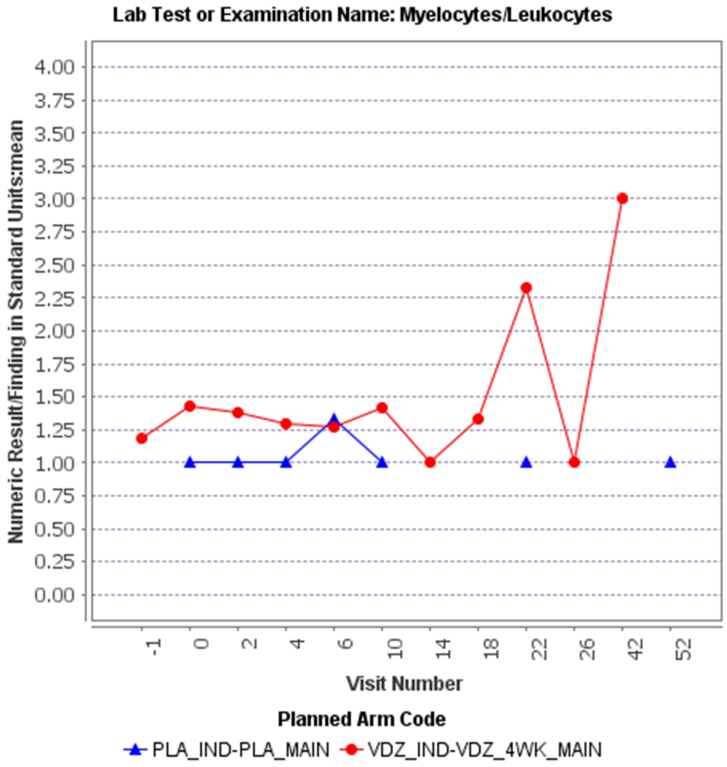


*based on average value from subjects at each time point

The periodicity of the increase in percent neutrophils in Figure 20 has a degree of regularity that suggests a correspondence to the dose interval.

In addition to automated white cell counts, limited data on manual differentials are available which suggest that, in addition to fluctuating increases of automatically counted neutrophils demonstrated above (average 6.4 %) (see table above), the number of myelocytes are increased in the vedolizumab q 4 weeks arm Figure 21:

Figure 21 Myelocytes relative to total leukocytes in C13007



The above graph shows the average number of myelocytes relative to the number of leukocytes. While the data points are few, a relative increase of peripheral myelocytes appears to be present in the vedolizumab arm which is consistent with mobilization of immature bone marrow cells.

A similar analysis as above (on total neutrophils and manual differentials) was performed for the every 8 week dosing of vedolizumab in study C13007. Interestingly, the hematological abnormalities affecting neutrophils are *not* seen with the lower dose. Also, a similar analysis was conducted on study C13006, and the potential signal could *not* be replicated.

In summary, the hematological data in C13007 would seem to suggest that vedolizumab may have off-target effects on the bone marrow based on the observed increased neutrophil and myelocyte counts in the peripheral blood when given every 4 weeks but not when given every 8 weeks. This effect was not observed in the Ulcerative Colitis study C13006. The results in C13007 q 4 weeks are, therefore, considered more likely spurious than not. Although the applicant has already demonstrated that CD34+

cells (a marker of immaturity) do not increase in response to the administration of vedolizumab in a small study in healthy volunteers, a determination of circulating CD34+ cells in response to the administration of vedolizumab in patients with IBD (rather than healthy volunteers) could further reassure us that this is indeed the case (see Section 1.4).

Mechanism

There are multiple possible mechanisms how vedolizumab could cause mobilization of myeloid derived cells from the bone marrow. Here we will limit ourselves to the suggestion of a possible role of α4β7 antagonism in the bone marrow. Although $\alpha_4\beta_1$ (VLA-4) has been assumed to represent the chief (or sole) functional α_4 integrin on stem/progenitor cells in the bone marrow, at least two papers report on a potential role for $\alpha_4\beta_7$ for hematogenic precursor cell homing to the bone marrow after transplantation in experimental animals (Katayama et al. 2004), (Tada et al. 2008). Homing of cells implies attachment to cell adhesion molecules and decreased attachment to the bone marrow stroma by blockade of this attachment mechanism could explain appearance of bone marrow derived cells in the peripheral blood.

Evidence for interference with mucosal defense/immune function outside the gut

Mucosal surfaces inside and outside the gastrointestinal tract maintain a constant vigilance against pathogens, mediated partly by continuous antigen sampling by antigen presenting cells (APCs), including dendritic cells (DCs), macrophages, and B-cells (Lawson, Norton, and Clements 2011). The integrins and their counter receptors play an important role in the trafficking of immunoglobulin A and G secreting cells to the mucosa in addition to their effects on T-cells. The traditional understanding is that the differential expression of the alpha4beta7 integrin ligand mucosal addressin cell-adhesion molecule 1 (MADCAM1) in the gut, and the alpha4beta1 (and alpha4beta7) integrin ligand vascular cell-adhesion molecule 1 (VCAM1) in other mucosal tissues fundamentally subdivides intestinal and non-intestinal tissues (Kunkel and Butcher 2003).

The applicant argues that vedolizumab is gut specific because the counter receptor for alpha4beta7 (MADCAM 1) is limited to the gut. In other words, effects on the extraintestinal mucosal immune defense should not occur or are negligible. This is in contrast with natalizumab where pleotropic broad bases effects are observed. This reviewer will quote published papers which suggest a role of MAdCAM 1 and alpha4beta7 integrins outside the gastrointestinal tract, and present adverse event data from the clinical studies that suggest that vedolizumab affects the mucosal immune defense outside the gastrointestinal tract and the skin, which, while not mucosa, also has a barrier function.[39]

[39] If not otherwise noted based on JumpStart Analysis Set MAED - General - C13007 07-17-2013 (Combined) and AE MedDRA - C13006 07-16-2013 (Combined) based on dm.sas7bdat and ae_maed.sas7bdat

Respiratory Tract Infections

In the natalizumab Crohn's disease trial, the incidence of nasopharyngitis was 11% in the natalizumab group and 6 % in the placebo group which was nominally significant (Targan et al. 2007). Interestingly, the results for natalizumab were similar, with 13 % and 7%, respectively (see Table 61)

Table 61 Adverse Events Table for Label (proposed by applicant)

(b) (4)

A review of the common adverse events suggests that patients that have received vedolizumab had approximately double the incidence of nasopharyngitis, sinusitis, and influenza. Oropharyngeal pain and cough are symptoms that may represent undiagnosed infections and these symptoms were also more frequently seen in patients receiving vedolizumab. These data suggest that vedolizumab may lower the resistance to viral and bacterial infections of the upper aerodigestive tract. Pruritus was also more common with vedolizumab than with placebo and this may be related to a possible effect of vedolizumab on the skin, which will further addressed below.

Mechanism and Information Request

Based on the above findings the clinical reviewers in conjunction with a CBER immunologist, Dr. Jennifer Reed, issued an information request to the applicant inquiring whether the following studies had been conducted:

1. In your preclinical studies of chronic α4β7 blockade, what measures of mucosal immunity of the respiratory tract have you evaluated? Appropriate measures could include IgA and IgM in nasopharyngeal samples or lung lavage, B and T lymphocyte recovery in lung lavage, cytokine evaluation in lavage or tissue homogenate.

2. Has there been any evaluation of α4β7 blockade in a respiratory challenge model, with for example, lipopolysaccharides (LPS) or influenza infection?

The applicant responded that no such studies (items 1. and 2.) had been performed.

Furthermore we asked:

3. In your preclinical study 502045, you found increased balantidium sp protozoa in some animals receiving α4β7 blockade. In what other studies has α4β7 blockade been linked with a change in gut flora?

The applicant contributed several non-clinical studies that answered this question. In summary, the applicant responded that existing data demonstrate that inhibition of α4β7 function can increase, decrease, or have no effect on gut flora. While MAdCAM 1 is traditionally thought to be expressed in low levels, if at all, outside the gastrointestinal tract, it appears that MAdCAM 1 plays an important role in the immune function of Nasal-Associated Lymphoid Tissue (NALT) (Csencsits, Jutila, and Pascual 1999). An impairment of NALT immune function by vedolizumab would explain the increased incidence of nasopharyngitis.

Paraesthesias and dysaesthesias

Study 13007 (Crohn's Disease)
Paresthesias and dysesthesias (MEDDRA High Level Term) were observed in 2.79 % of 718 vedolizumab treated patients in study C13007 and there were no reports in 148 placebo treated patients. This corresponds to an odds ratio of 8.7 (95 % CI 0.5 – 144.9) with a nominal p-value of 0.035[40].

Study 13006 (Ulcerative Colitis)

Paresthesias and dysesthesias were approximately equally distributed between the vedolizumab and placebo arms, with an incidence of 1.2 % and 1.3 %, respectively.

[40] This is an exploratory analysis and the CI and p-values are given for information only. A continuity correction of 0.5 was applied.

Mechanism

It is known that the abnormal expression of integrins or their ligands, is associated with degenerative, inflammatory, and malignant disorders of the peripheral nervous system (PNS). Integrins also participate in the complex interactions that promote repair of the PNS (Previtali et al. 2001).
How vedolizumab could promote neuropathy, if it indeed does, is unclear, however, a drug-induced autoimmune process, as is sometimes seen with other biologics, is a possibility (Ramos-Casals et al. 2010, -). Neuropathies occur not infrequently in auto-immune diseases and they can occur also occur in inflammatory bowel disease where they are, however, uncommon (Figueroa et al. 2013).

There was no apparent signal for paresthesias in the natalizumab multiple sclerosis (MS) trials which can probably be explained by the fact that these symptoms are frequently reported by MS patients. The signal of possible neurotoxicity of vedolizumab in study C13007 (but not in study C13006) is important because drug-induced neuropathies need to be recognized early to avert more long-lasting and progressive impairment.

Skin conditions

Study 13007 (Crohn's Disease)

The incidence of "apocrine and eccrine gland disorders" was 2.65 % in the vedolizumab group and 0 % in the placebo group in C13007 corresponding to an odds ratio of 8.3 (95 % CI 0.5 – 137.9) with a nominal p-value of 0.058.

The MEDDRA High Level Group Term (HLGT) for the High Level Term (HLT) "apocrine and eccrine gland disorders" is "skin appendage conditions". The incidence for vedolizumab was 6.3 % and for the placebo arm 2.0 % with an odds ratio of 3.2 (95 % CI 1.0 -16.5) and a nominal p-value of 0.046.

Study 13006 (Ulcerative Colitis)

Adverse events coded with the HLGT "epidermal and dermal conditions" were overrepresented in the vedolizumab group (n= 576) with 14.7 % versus 8.1 % in the placebo group (n=149). The odds ratio was 2.0 (95 % CI 1.0 – 4.0) corresponding to a nominal p-value of 0.041.

The HLT "apocrine and eccrine gland disorders" was also more frequently associated with vedolizumab than placebo, 2.1 % vs. 0 %v in this study (OR 6.6. 95 % CI 0.4 - 112.5; nominal p–value 0.14).

Mechanism

How vedolizumab would increase the incidence of "skin appendage conditions" and "epidermal and dermal conditions" is unclear. Folliculitis (a preferred MEDDRA term) was seen in 1.1 % of patients treated with vedolizumab in C13007and was not reported

in the placebo group. Folliculitis and related conditions could be caused by a decreased immune surveillance mediated by T-cell dysfunction (Robert and Kupper 1999). It has been shown that the integrins alpha4beta7 and alphaEbeta7 contribute to epidermotropism of T-cells during skin inflammation (Schechner et al. 1999), (Sun et al. 2002). Blockade of alpha4beta7 by vedolizumab may interfere with the control of skin inflammation in currently unknown ways.

Summary and Regulatory Relevance

Review of hematological laboratory data and adverse events seems to show that vedolizumab has off-target effects affecting the upper respiratory tract, the skin and, perhaps, the peripheral nervous system and bone marrow. Some of these adverse events appear to be, at this time, of minor importance, however, they show that the use of the terms (b) (4) for vedolizumab is not warranted, and the applicant should not use this descriptor for promotional materials and journal publications.

Determination of IgA and IgM in nasopharyngeal samples or lung lavage, B and T lymphocyte recovery in lung lavage, and cytokine evaluation in lavage or tissue homogenate could be included in an observational post marketing study in order to elucidate the mechanism for the increased incidence of upper respiratory tract infections, specifically, nasopharyngitis. This Reviewer recommends that (pending discussion with reviewers in the Office of Surveillance and Epidemiology - Divisions of Pharmacovigilance, Epidemiology, and Risk Management) determination of IgA and IgM in nasopharyngeal samples should be included as a substudy in the proposed observational postmarketing study (see Section 1.4).

The incidence of “paraesthesias and dysaesthesias” in C13007 was 2.8 % in the vedolizumab arm and 0 % in the placebo arm with an odds ratio of 8.7 and relative risk of 8.5 (and a corresponding nominal p-value of 0.035). This could be a signal of considerable importance even if it was not seen in study C13006 because neurotoxicity is not implausible: Many biologic agents, so far mostly anti-TNF agents, have been associated with paradoxical induction of autoimmune processes, and these autoimmune processes may present as peripheral neuropathy caused by demyelination or vasculitis (Ramos-Casals et al. 2010).

This reviewer recommends that “paraesthesias and dysaesthesias” and “skin conditions” should be considered (pending discussion with reviewers in the Office of Surveillance and Epidemiology - Divisions of Pharmacovigilance, Epidemiology, and Risk Management) to be included as adverse events of special interest with targeted neurological and dermatological investigations in the proposed post-marketing observational study or in an enhanced pharmacovigilance plan to further evaluate and characterize the potential risk of neuropathy and dermopathy with vedolizumab. (See Section 1.4)

This reviewer recommends that the label call attention to an increased incidence of “epidermal and skin conditions” based on the strength of the evidence, and to

"paraesthesias and dysaesthesias" observed in C13007 based on the potential seriousness of the condition. (See Section 9.2)

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8 Postmarket Experience

There is no postmarket experience with this drug because it is not approved at the time of this review.

9 Appendices

9.1 Literature Review/References

See footnotes.

9.2 Labeling Recommendations

The Applicant's proposed label included all the required sections and was appropriately formatted. The Applicant's proposed label was reviewed, and revisions and comments were communicated to the Applicant on November 22, 2013.

Major clinical issues related to the label included:

- Specific information was added in *5 Warnings and Precautions* that anaphylaxis has been reported with ENTYVIO administration
- Specific information was added in *5 Warnings and Precautions* that serious infections have been reported in patients treated with ENTYVIO
- The immunogenicity of vedolizumab was underestimated in the label, and significant revisions to this section will be communicated to the Applicant
- Revisions were made to section 12.1 Mechanism of Action to remove language indicating that vedolizumab is (b) (4) and to provide more detailed information on its relative (b) (4)

In addition to the above, this reviewer recommends the following label revisions:

- The label should call attention to an increased incidence of "epidermal and skin conditions" based on the strength of the evidence, and to "paraesthesias and dysaesthesias" observed in C13007 based on the potential seriousness of the condition.
- For Crohn's disease, the labeling should describe the time course for achieving clinical remission in CD based on the clinical trial data and should avoid the term "maintenance".

All labeling recommendations are subject to formal negotiations with the Applicant. The final approved labeling will be appended to the approval letter.

9.3 Advisory Committee Meeting

A summary of the Advisory Committee Meeting is provided below:

Efficacy in Crohn's Disease (CD):

1. Evidence for vedolizumab efficacy for CD induction is provided by one trial but not supported by a second trial that primarily enrolled a refractory population. Evidence for vedolizumab efficacy for CD maintenance is provided in one trial.

   a. **VOTE**: Do the available data support the efficacy of vedolizumab for the proposed CD induction indication? (please explain your vote)

      Vote: YES = 12 NO = 9 ABSTAIN = 0

      Committee Discussion: *Majority of the committee voted that the data support the efficacy of vedolizumab for the proposed CD induction indication and thought that the 10 week data were convincing. Those voting "No" commented that data presented by FDA showed that only one primary endpoint was met and the totality of data did not meet the threshold to support the efficacy for induction. Please see the transcript for details of the committee discussion.*

   b. **VOTE**: Do the available data support the efficacy of vedolizumab for the proposed CD maintenance indication? (please explain your vote)

      Vote: YES = 19 NO = 1 ABSTAIN = 1

      Committee Discussion: *The committee agreed that the available data support the efficacy of vedolizumab for the proposed CD maintenance indication. The committee member who abstained stated that he abstained from voting due to his lack of knowledge of how the issues with the drug during induction would affect the maintenance. One member who had originally voted "No" subsequently noted during the explanation of the vote that she wanted to vote "Yes." The vote count above records her vote as "No". Please see the transcript for details of the committee discussion*

   c. **DISCUSSION:** Please discuss if further studies are needed and what those studies should address.

      Committee Discussion: *Committee members commented that the demand for other treatments for CD is high and additional trials would increase cost and delay the drug availability. Please see the transcript for details of the committee discussion*

Safety:

2. **VOTE:** Considering the currently available nonclinical and clinical data, has the applicant adequately characterized the potential risk of PML with vedolizumab to support approval? (please explain your vote)

Vote: ***YES = 21*** ***NO = 0*** ***ABSTAIN = 0***

Committee Discussion: *The committee agreed that the applicant has adequately characterized the potential risk of PML with vedolizumab with the current data to support approval. Members noted that continued monitoring and observation are still necessary to assess the potential risk of PML and the occurrence of serious infections. Please see the transcript for details of the committee discussion.*

3. **VOTE:** If vedolizumab is approved, should concomitant immunosuppressants be limited to a specific duration (e.g., during induction only)? (please explain your vote)

Vote: ***YES = 1*** ***NO = 19*** ***ABSTAIN = 1***

Committee Discussion: *The committee agreed that concomitant immunosuppresants should not be limited to a specific duration. The member who voted "Yes" commented that she wants to make sure that there was language in the labeling that reflects what was done in the clinical program. The member who "Abstained" noted that he hopes there is no restriction and would like to see how the drug is used in real practice. Please see the transcript for details of the committee discussion.*

Benefit-Risk Assessment for UC:

4. **VOTE (choose a, b, or c):** Based on currently available efficacy and safety data, do the benefits outweigh the potential risks of vedolizumab (in particular, PML) to support approval for:
   a. the proposed UC population that have failed steroids or immunosuppressants or TNFα-antagonists?
   b. patients that have failed immunosuppressants or TNFα-antagonists (i.e., the indicated population would not include patients that failed steroids only)?
   c. neither a nor b.

Vote: ***A = 13*** ***B = 8*** ***C = 0***

Committee Discussion: *Majority of the members agreed that the benefits outweigh the risks to support the approval for the proposed UC population that have failed steroids or immunosuppresants or TNF α-antagonists and commented that restrictions would be burdensome in clinical practice. Members voting "B" noted that patients failing steroids have other options. One member who had originally voted "B" subsequently noted during the explanation of the vote that he wanted to vote "A." The vote count above records his vote as "B". Please see the transcript for details of the committee discussion.*

Benefit-Risk Assessment for CD:

5. **VOTE (choose a, b, or c):** Based on currently available efficacy and safety data, do the benefits outweigh the potential risks of vedolizumab (in particular, PML) to support approval for:
   a. the proposed CD population that have failed steroids or immunosuppressants or TNFα-antagonists?
   b. patients that have failed immunosuppressants or TNFα-antagonists (i.e., the indicated population would not include patients that failed steroids only)?
   c. neither a nor b.

   Vote: A = 14 B = 6 C = 1

   Committee Discussion: *The majority of the committee agreed that the benefits outweigh the potential risk to support approval for the proposed CD population that have failed steroids or immunosuppressants or TNFα-antagonists for the same reasons as UC. Those voting "B" noted that the margin between risk and benefit in this population is smaller, than in UC. One member who voted "C" commented that immunosuppressants and anti-TNF agents are well established and vedolizumab appears to be slow to work. Please see the transcript for details of the committee discussion*

Safety and Risk Mitigation Strategy Considerations:

6. **DISCUSSION:** If vedolizumab is approved for the proposed UC or CD indications:

   a. Discuss what post-market risk mitigation strategies beyond labeling, if any, would be needed to ensure that the product's benefits outweigh its risks.
   b. Discuss what additional safety studies or trials should be conducted, if any.

   Committee Discussion: *Committee members commented that it is important to quantify PML risks and to monitor other infections in addition to PML. Members also noted that post-market risk mitigation strategies should not be burdensome for the practitioners. Self reported adverse events registries could also be considered. Please see the transcript for details of the committee discussion.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KLAUS T GOTTLIEB
12/30/2013

ANIL K RAJPAL
12/30/2013
I concur with Dr. Gottlieb.

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125476
Priority or Standard	Priority
Submit Date(s)	June 20, 2013
Received Date(s)	June 24, 2013
PDUFA Goal Date	February 18, 2014
Division / Office	Division of Gastroenterology and Inborn Error Products/Office of Drug Evaluation III
Reviewer Name(s)	Laurie Muldowney, MD
Review Completion Date	
Established Name	Vedolizumab
(Proposed) Trade Name	Entyvio
Therapeutic Class	Integrin Receptor Antagonist
Applicant	Takeda
Formulation(s)	Lyophilized powder for injection
Dosing Regimen	300 mg infused intravenously over approximately 30 minutes at 0, 2, and 6 weeks, and then every 8 weeks thereafter
Indication(s)	reducing signs and symptoms,

	inducing and maintaining clinical response, clinical remission, and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist
Intended Population(s)	Adult patients with moderately to severely active ulcerative colitis as defined by the Mayo Score

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer that vedolizumab be approved for the indication of:

inducing and maintaining clinical response and remission, improving endoscopic appearance of the mucosa, and achieving (b) (4) corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either immunomodulators or tumor necrosis factor-alpha (TNFα) antagonist.

1.2 Risk Benefit Assessment

Moderately to severely active ulcerative colitis (UC) is a serious chronic disease which has a substantial impact on patients' quality of life. Patients with UC experience recurrent episodes of bloody mucoid diarrhea and abdominal pain which may be followed by quiescent periods. Patients may also exhibit systemic symptoms including fever, malaise, and weight loss; and severe colitis can result in ischemic colitis requiring surgical colectomy. While colectomy is considered curative in UC, it is associated with significant morbidity, including recurrent pouchitis in up to 25% of patients, fecal incontinence, and female infertility. Finally, patients with long-standing UC are at increased risk for colorectal cancer which is thought to be related to chronic inflammation.

Available treatments for moderate to severe disease include corticosteroids, immunomodulators, and monoclonal antibodies targeting TNF-α (i.e., infliximab, adalimumab, and golimumab). Limitations exist, however, and many patients are unable to achieve sustained remission despite optimizing currently available therapies. Other patients develop intolerance to or side effects from their current treatment regimens. Additional treatment options for patients with moderately to severely active UC, particularly those who have failed prior anti-TNF therapy, is needed.

Review of the current Application reveals that the benefit of vedolizumab for reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have failed prior therapies has been adequately demonstrated, and the benefit outweighs the risks associated with the use of the drug product.

The data provided by the applicant to support this indication was from a single Trial, C13006, a phase 3, randomized, double-blind, placebo-controlled trial in 895 patients with moderately to severely active UC. This trial was conducted under a single protocol but designed and analyzed as 2 separate studies: C13006 Induction Study and C13006 Maintenance Study. The results were highly reliable, statistically strong, and internally consistent, supporting the efficacy of vedolizumab from a single study.

Induction Study Results Summary

According to my review of the clinical data, the applicant demonstrated that vedolizumab is effective in meeting its primary induction endpoint, clinical response at Week 6, where response is defined as a reduction in the complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point. The proportion of patients in clinical response at Week 6 was significantly greater in the vedolizumab group (47.1%) relative to placebo (25.5%). The difference from placebo was 21.7% (95% CI: 11.6, 31.7; p< 0.0001). Vedolizumab appeared to be slightly less effective in the subgroup of patients who previously failed TNFα agents, however, even in these more difficult to treat patients, vedolizumab performed better than placebo. The applicant's results were internally consistent across a variety of subgroups, including age, gender, race, disease duration, geographic region, and baseline disease activity. While the study was not powered for key subgroup analyses and there was no multiplicity adjustment, because they were consistent with the overall results this reviewer feels they can generally be believed.

The applicant demonstrated evidence of effectiveness for the secondary Induction endpoint, the proportion of patients with clinical remission at Week 6. Thirty-eight patients (16.9%) in the vedolizumab group achieved clinical remission, compared to 8 patients (5.4%) in the placebo group. The difference from placebo was 11.5% (p = 0.0009).

The prespecified secondary endpoint for mucosal healing was defined as Mayo endoscopic subscore of ≤ 1 point. Using the prespecified definition, 40.9% of patients in the vedolizumab treatment group achieved mucosal healing, compared with 24.8% of patients receiving placebo, a 16.1% treatment difference (p = 0.0012). The applicant provided no histologic data to support a labeling claim for "mucosal healing", however; the data provided would support a labeling claim of "improved endoscopic appearance of the mucosa".

Maintenance Study Results

The applicant demonstrated substantial evidence of effectiveness for the primary endpoint for the Maintenance Study, the proportion of patients with clinical remission at Week 52, where clinical remission was defined as total Mayo score of ≤ 2 points with no

individual subscore > 1 point. Both vedolizumab dosing regimens were independently significantly better than placebo, using the applicant's definition for remission. In the Q8W dosing group, the difference from placebo was 26.1%, and in the Q4W group, the difference was 29.1%, with $p < 0.0001$ for both groups. Again, sensitivity analyses and subgroup analyses performed by the applicant (e.g., age, gender, race, duration of disease, geographic region, and baseline disease activity, anti-TNF users and failures) were generally consistent and supported the efficacy of vedolizumab in maintaining clinical remission.

In addition, the applicant adequately demonstrated that vedolizumab is effective at maintaining clinical response. A significantly higher proportion of vedolizumab treated patients in both dosing regimens were in clinical response at Week 52 compared with patients who received placebo ($p < 0.0001$).

As in the Induction Study, the prespecified secondary endpoint for mucosal healing during the Maintenance Study was defined as Mayo endoscopic subscore of ≤ 1 point. Using the prespecified definition, there was a 32.0% and 36.3% treatment difference favoring vedolizumab (Q8W and Q4W, respectively) over placebo. When analyzing only patients who had endoscopic subscore of 0, the results remain statistically significant. Given the lack of histologic data to support a labeling claim for "mucosal healing", the data provided would support a labeling claim of improved "endoscopic appearance of the mucosa".

Finally, the applicant provided data also provided sufficient evidence to demonstrate that vedolizumab is effective in achieving corticosteroid-free clinical remission. Approximately 58% of patients in the Maintenance ITT population were receiving corticosteroids at Week 6, and a significantly higher proportion of patients from both vedolizumab arms were in clinical remission and on no corticosteroids at Week 52 than from the placebo group ($p = 0.0120$ for Q8W; $p < 0.0001$ for Q4W). The sponsor's definition for corticosteroid free remission did not specify a minimum duration of time for which patients were required to be corticosteroid free, however, those patients who achieved sponsor defined corticosteroid-free remission at Week 52 were corticosteroid free for an average of 270 days (260 days ITT placebo, 267 days Q8W, and 274 days Q4W) compared to approximately 100 days (110 days ITT placebo, 97 days Q8W, and 94 days Q4W) for those who did not achieve this endpoint. In addition, 2 exploratory analyses were completed to analyze the proportion of patients who achieved continued remission and were corticosteroid free for 90 days and 180 days prior to Week 52, and these results were consistent with the secondary endpoint results.

Dosing

The applicant's dosing recommendations for vedolizumab are a dose of 300 mg administered as an IV infusion over 30 minutes at Week 0, Week 2, Week 6, and Q8W thereafter. The dosing recommendations go on to state that if clinical response is not

achieved by Week 6, or if patients lose response when dosed Q8W, dosing Q4W may be considered.

The initial dosing recommendations are supported by data from C13006. Vedolizumab 300 mg was effective at inducing and maintaining clinical response and remission when administered at Week 0, Week 2, Week 6, and Q8W. Vedolizumab was also effective at maintaining clinical response and remission when dosed Q4W. Given that neither dosing regimen showed a clear efficacy or safety advantage, it is appropriate to treat with the lowest effective dose

The applicant's recommendation to consider dose escalation is based on PK data (vedolizumab trough data and PK modeling from Phase 3 studies) as well as information derived from Studies C13006 and C13008. An increase in dosing frequency for patients who fail to achieve clinical response by Week 6 was not formally studied as part of the applicant's Phase 3 program, however, and Study C13006 was not powered to directly compare the Q4W and Q8W doses. Study C13008 was open-label and not designed to assess efficacy endpoints, so efficacy data from this study should be considered with caution. Additional data is required to support the dosing escalation recommendations by the applicant.

Safety

This reviewer believes vedolizumab has been shown to be safe for its intended use as recommended in the labeling. Overall, the safety profile of vedolizumab was adequately characterized during the clinical development program.

The proportion of patients with at least 1 AE was 84% in patients receiving vedolizumab, compared to 78% in patients receiving placebo. The most commonly reported AEs which occurred more commonly in the vedolizumab treated patients were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, and cough.

Nineteen percent (19%) of patients receiving vedolizumab throughout reported serious adverse events (SAEs) compared to 13% of patients who received placebo only. Serious infection AEs and those considered drug-related occurred with similar frequency between the vedolizumab and placebo groups (serious infection AE 4% and 3% respectively, and drug-related SAE 3% and 2%, respectively). The most frequently reported SAE (≥ 1% of the VDZ/VDZ population) in UC patients was related to underlying IBD (ulcerative colitis).

A higher proportion of patients in vedolizumab treated groups reported 1 or more infectious AE, than in the placebo groups, and this was largely driven by an increased rate of infections involving the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection) which were mild to moderate in

severity. Serious infections were reported by 20 patients in C13006 and at a similar frequency between treatment groups (3% placebo only group; 2% vedolizumab).

Two cases of potential drug related liver toxicity were reported, one in Study C13006 and a second case in the C13008 120-day safety update. Case report information provided for both indicate a possible drug or autoimmune etiology. Additional information was requested of the applicant, including information on any additional cases of hepatitis or liver injury where drug induced or autoimmune hepatitis were considered in the differential was requested. Clinically significant liver injury has occurred with natalizumab use, and this potential adverse event should be included in the labeling and closely monitored in the postmarketing setting with consideration for enhanced pharmacovigilance. An addendum to this review will be provided following response from the applicant to our information request and further internal discussion.

Since 2007, the vedolizumab clinical development program included a Risk Assessment and Minimization for PML (RAMP) program. The RAMP program was thorough, and no cases of PML were identified through the 120 day safety data cutoff. This included 903 patients exposed to 24 or more vedolizumab infusions with 4-weeks of follow up and approximately 80% of whom received prior immunosuppressant therapy. Less than 1% of patients tested positive for JC viremia, and JCV antibody testing was not included in the RAMP program. There were 0 cases of PML identified during the vedolizumab clinical development program to date.

Outstanding Issues

The Applicant adequately demonstrated the efficacy of vedolizumab and that the benefit of vedolizumab outweighs its potential risks for adult patients with moderately to severely active ulcerative colitis. Outstanding issues related to vedolizumab for ulcerative colitis include:

- The key safety issue is the potential risk of progressive multifocal leukoencephalopathy (PML). There is uncertainty about the adequacy of the safety database to provide an acceptable pre-marketing assessment of this risk of PML or if continued risk evaluation and mitigation strategies (e.g., REMS) are needed in the postmarketing setting. This will be discussed at the Advisory Committee.
- Two potential cases of drug related liver injury were reported. Additional information is forthcoming from the Applicant, and an addendum to this review will be provided. Enhanced pharmacovigilance in the postmarketing setting may be needed to ensure any future cases are captured.
- Although a relationship between concomitant immunosuppressive therapies with infections was not found, there remains the concern that the risk of infections and of PML might be higher with concomitant immunosuppressive therapies. In the vedolizumab trials, these considerations led to the requirement that concomitant immunosuppressants will not be allowed beyond the induction phase (e.g., 6

weeks) in the US trials. We question whether the labeling should have similar restrictions. Similarly, due to the potential risk for PML, vedolizumab use was limited to patients who failed immunomodulator or TNFα antagonist therapy in US trials, whereas outside the US prior corticosteroid failure was sufficient for inclusion. We question if vedolizumab should be indicated only for those patients who failed immunomodulator and/or TNFα antagonist therapy, or if prior corticosteroid failure should be sufficient.

Reviewer Comments: While there were no cases of PML in the premarketing safety database, there is still uncertainty as to whether the database was sufficient to rule out an acceptable risk. Until that determination is made, this reviewer recommends vedolizumab be labeled for patients who failed immunomodulator or TNFα antagonist therapy. These issues will be discussed at the Advisory Committee on December 9, 2013, and I will provide an addendum to this review, pending the Advisory Committee recommendations.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The primary serious risk of harm relevant to REMS considerations is the potential risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Natalizumab, an integrin antagonist approved in the treatment of multiple sclerosis and Crohn's disease, is associated with an increased risk for PML. No cases of PML have been reported in the vedolizumab clinical development program, out of 3326 patients exposed, however a theoretical risk remains.

The applicant proposes a REMS with medication guide and communication plan (b) (4) as the risk management strategy for vedolizumab.

A variety of approaches have been utilized by CDER in the past to address PML risk in other drug products, from PML specific labeling to REMS with elements to assure safe use (ETASU). Most of the products using only PML-explicit labeling to manage PML risk are products used in oncology and transplantation medicine, where there may already exist an underlying risk for opportunistic infections and PML. Natalizumab includes PML specific labeling in a Black Box Warning and has a required REMS with ETASU. The REMS requirement for natalizumab was based on the determination that there was a definitive risk for this serious, and often fatal condition in a population previously not at risk.

Given that there have been no cases of PML detected in the vedolizumab clinical development program to date, the risk of PML with vedolizumab remains a theoretical

risk. One could argue that labeling alone may be an appropriate strategy. Alternatively, an underlying risk for PML has not been seen in patients with UC and CD on other therapies, excluding natalizumab, and the risk for PML has not been entirely ruled out, with the safety database provided by the sponsor. While nonclinical data is reassuring in demonstrating the selectivity of vedolizumab's binding to the α4β7 integrin, the mechanism by which PML develops in patients administered integrin antagonist products is not completely understood and clinical data is needed to estimate risk.

It is unclear what evidentiary threshold we may be comfortable with, to rule out a specific level of risk of PML in these patients with a reasonable level of certainty. A critical question which will drive the selection of the optimal risk management strategy for vedolizumab is: considering the totality of the non-clinical and clinical evidence, how many vedolizumab patients need to be studied for how long to rule out the risk of PML with a reasonable level of certainty. If it is determined that the Applicant has not ruled out the potential of PML with a reasonable level of certainty, a REMS with ETASU may be needed. This approach will increase the burden on patients, prescribers, pharmacies, and infusion centers, and it is possible that vedolizumab may not address the unmet medical need in UC to the fullest extent possible. It would be important to discontinue the REMS program once a sufficient number of patients have been exposed, assuming no cases of PML arise.

Reviewer Comments: These issues will be discussed at the Advisory Committee on December 9, 2013, and I will provide an addendum to this review, pending the Advisory Committee recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review, the following Postmarket Requirements and Commitments are recommended:

The Clinical Pharmacology review team recommends the following post marketing commitment (PMC) studies:

- A study to reanalyze banked immunogenicity serum samples from ulcerative colitis trial C13006 and Crohn's disease trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference. This recommendation is based on the finding of inadequate assessment of immunogenicity incidence in the current BLA.
- Evaluate the disease-drug-drug interaction (DDDI) potential between vedolizumab and other CYP substrates. This recommendation is based on the current understanding that CYP enzymes expression is suppressed by inflammatory cytokines associated with inflammatory conditions, and they can normalize upon improvement of the inflammatory conditions. We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of UC or CD, an inflammatory disease condition, on the exposure of CYP

substrate drugs (i.e., the disease drug interaction). Such study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the DDDI.

The following study is recommended from the Pediatric and Maternal Health Staff as a PMC:

- Conduct a milk-only lactation trial in lactating women receiving vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk using a validated assay in order to appropriately inform the Nursing Mother's subsection of labeling

In addition,

- The applicant has requested a Waiver of Pediatric Study for pediatric patients from birth to (b) (4) and a Deferral of Pediatric Study for pediatric patients (b) (4) to < 18.

Reviewer comment: We generally have waived requirements for pediatric studies of UC treatments in children under the age of 5 years due to the low UC incidence in that age group. The final determination of pediatric waiver and deferral will be made upon presentation to the Pediatric Research Committee (PeRC) as part of the review of this BLA for moderately to severely active UC in adults.

2 Introduction and Regulatory Background

Ulcerative colitis (UC) is a chronic relapsing inflammatory disease of the rectal and colonic mucosa, which is characterized by clinical remissions and exacerbations resulting from intestinal inflammation. The typical age of onset for UC is between the ages of 15 and 30, and over 450,000 people in the United States (US) may be affected. (*Loftus EV. Inflammatory Bowel Disease, 2007; 13(3):254-261)* While the pathogenesis of UC is not completely understood, abnormal leukocyte trafficking to the GI mucosa is believed to be an important component leading to colonic inflammation.

Symptoms can vary depending on the severity of inflammation and extent of disease; however, patients typically experience recurrent episodes of rectal bleeding and diarrhea, often associated with crampy abdominal pain and tenesmus. Symptoms are often followed by periods of remission, which may be spontaneous or as a result of treatment. Patients may also exhibit systemic symptoms including fever, malaise, and weight loss; and severe colitis can result in ischemic colitis requiring surgical colectomy. Colectomy is considered curative in UC, but it is associated with significant morbidity, including recurrent pouchitis in up to 25% of patients, fecal incontinence, and female

infertility. Finally, patients with long-standing UC are at increased risk for colorectal cancer. The goals of UC treatment are to induce and maintain remission of clinical symptoms and mucosal inflammation in order to improve quality of life, decrease hospitalizations, and reduce the risk of surgery and colon cancer. (*Hoentjen F, et al., Curr Gastroenterol Rep 2011;13:475-485*)

The treatment options for UC are dictated by the severity of clinical symptoms and the anatomic extent of disease. Patients with mild to moderate UC are typically treated with topical and oral aminosalicylates, as well as topical steroids. Oral corticosteroids may be required in patients who are refractory to these treatments or who are systemically ill and require more rapid treatment. Immunomodulators such as azathioprine and mercaptopurine can be considered for patients not responding to or dependent on oral corticosteroids and for those who relapse on aminosalicylates.

Available treatments for moderate to severe disease include corticosteroids, immunomodulators, and monoclonal antibodies targeting TNF-α. There are three currently approved anti-TNF agents for UC, infliximab, adalimumab, and golimumab. These agents provide an important treatment option for patients with moderate to severe UC who have failed other therapies; however none has been shown to achieve sustained remission in more than 30% of patients (*Hanauer et al 2002, Sandborn et al 2005*); and in clinical trials, patients who had failed 1 anti-TNF agent had a significantly lower response to subsequent anti-TNF therapy. *(Thomson AB 2012;18(35) World J Gastro).*

Limitations remain in the treatment of UC, and despite optimizing treatment with currently available therapies, patients continue to have symptoms or develop intolerance to or side effects from their treatment regimens.

2.1 Product Information

Vedolizumab is a humanized IgG1 monoclonal antibody that belongs to the class of integrin antagonist drugs. Vedolizumab specifically targets the human lymphocyte integrin α4β7, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) which is expressed on the endothelium of intestinal vasculature.

Established name:	vedolizumab
Proposed trade name:	Entyvio
Pharmacologic class:	Integrin Receptor Antagonist

Dosage Form and Strength:	lyophilized powder for injection available in sterile single-use vials containing 300mg vedolizumab for intravenous infusion

Applicant's proposed indications for ulcerative colitis:

- Vedolizumab is indicated for reducing signs and symptoms, inducing and maintaining clinical response, clinical remission, and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

Applicants proposed dosing regimens:

- 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently available approved treatments for moderately to severely active UC appear in Table 1.

Table 1: Currently Available Treatments

Treatment	Drug Class	Indication	Main Safety Issues for Anti-TNF Agents
Remicade® (infliximab)	Anti-TNF	reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.	- increased risk of serious infections leading to hospitalization or death, including tuberculosis, bacterial sepsis, invasive fungal infections and infections due to other opportunistic pathogens - lymphoma and other malignancies, some fatal - hepatosplenic T-cell lymphoma
Humira® (adalimumab)	Anti-TNF	Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.	
Simponi (golimumab)	Anti-TNF	indicated in adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: o inducing and maintaining clinical response o improving endoscopic appearance of the mucosa during induction o inducing clinical remission o achieving and sustaining clinical remission in induction responders	

2.3 Availability of Proposed Active Ingredient in the United States

Vedolizumab is a new molecular entity (NME) that is not approved or marketed in the United States

2.4 Important Safety Issues With Consideration to Related Drugs

Tysabri (natalizumab) in the only currently marketed integrin antagonist. It is approved for inducing and maintaining clinical response and remission in adult patients with

moderate to severely active Crohn's Disease (CD) with evidence of inflammation and who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF-α.

Tysabri contains a boxed warning that it increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking Tysabri who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving Tysabri as monotherapy.

As per the current label for Tysabri, three factors that are known to increase the risk of PML in Tysabri-treated patients have been identified:
(1) Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than (b) years of TYSABRI treatment.
(2) Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
(3) The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.

Because of the risk of PML, Tysabri has a REMS requirement composed of a Medication Guide, Communication Plan, and Elements to Assure Safe Use including prescriber, pharmacy, and patient registration. Tysabri is available only through a special restricted distribution program called the CD Tysabri Outreach Unified Commitment to Health (TOUCH™) program. This program includes infusion site training and maintains a computerized database that captures enrollment, patient tracking, and drug distribution.

In addition to increasing the risk of PML, hypersensitivity reactions, including anaphylaxis, have occurred in patients receiving Tysabri and were more frequent in patients with antibodies to Tysabri. Tysabri may also increase the risk for infections, including urinary tract infection, pneumonia, and gastroenteritis.

At the time of approval for CD, one of the post-marketing commitments (PMCs) was for a prospective observational study (CD INFORM) that specified that at least 2,000 CD patients must be enrolled, and that a least 1,000 patients must have two years of Tysabri treatment. CD INFORM was designed primarily to determine the incidence and pattern of serious and/or clinically significant infections, malignancies, and other serious adverse events (SAEs) in patients with Crohn's disease (CD) treated with natalizumab; the main safety outcome of interest in CD INFORM is PML. At the time of this review, the accrual of the study has been limited by the use of the marketed product in CD, and a total of only 187 subjects have been enrolled. Additional data is not yet available.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clinical development of vedolizumab began in 1998, and IND 9125 was opened in June 2000 to initiate clinical development in the US. In January 2006, development of vedolizumab was placed on clinical hold due to concerns that integrin antagonists might predispose patients to progressive multifocal leukoencephalopathy (PML). This stemmed from the market withdrawal of natalizumab, following 2 cases of confirmed PML in patients receiving the drug to treat MS and one reported case in a patient treated for Crohn's disease. All integrin antagonists under development in the US at that time were placed on clinical hold. The clinical hold on IND 009125 was lifted in July 2007 with the implementation of an active screening and monitoring program. Multiple subsequent regulatory meetings, including an Advisory Committee (AC) meeting, have focused on risk minimization and safety monitoring related to potential PML risk, and the major agreements and recommendations are summarized below.

A Joint Meeting of the Gastrointestinal Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee to evaluate intravenous vedolizumab for treatment of Inflammatory Bowel Disease (induction and maintenance of Crohn's Disease and Ulcerative Colitis) and the risk of PML was held on July 20, 2011. The purpose of this closed session Advisory committee was to seek the committee's recommendations regarding the Phase 3 study design for vedolizumab, including the number of patients and duration of study needed to exclude the risk of PML. The following recommendations and responses were provided by the expert committee, in response to 4 questions:

- The committee voted 12 to 5, with one abstention, that the available nonclinical and human pharmacodynamic data for vedolizumab do not provide assurance of less risk of PML than natalizumab.
- The committee commented on an acceptable safety database size for pre-approval assessment of PML risk in patients with CD and UC. No consensus was reached, however, the AC strongly expressed that the duration of exposure is important and that 24 months could be considered as the minimum duration timeframe. The majority of the committee felt that increasing the sample size has merit.
- The committee voted 15 to 2, with one abstention, that the available nonclinical and clinical data do not support making the entry criteria less stringent for vedolizumab phase 3 studies (i.e., allow entry of patients that have not yet been treated with TNFα antagonists or immunosuppressants).
- The committee voted 17 to 0, with one abstention, that restrictions on concomitant immunosuppressants (prohibited beyond the induction phase of vedolizumab treatment) should not be made less stringent.

Based on the AC recommendations and over the course of several meetings between the sponsor and FDA, the following major agreements were made relating to the risk of PML with this class of therapy:

- patient screening and monitoring: a screening baseline neurologic exam with exclusion of those with abnormal findings, education of site personnel and patients, and updated informed consent documents
- selection criteria: patients enrolled in phase 3 studies in the United States were required to meet the stricter requirement of inadequate response or intolerance to immunosuppressants or TNFα antagonists, rather than immunosuppressants, TNFα antagonists, or corticosteroids
- concomitant medications: in the US, patients in phase 3 studies were allowed concomitant steroid use for one and one-half years, with tapering at week 6 in patients that are in clinical response, or when clinical response is achieved. In addition, concomitant immunosuppressant use was allowed for up to 6 weeks in Phase 3 studies, but must be otherwise prohibited.
- safety database: the safety database at the time of original BLA submission must include data on at least 900 patients that received ≥ 24 infusions, with a minimum of 4 weeks of follow-up after the last infusion. The Division anticipated this would result in ~1000 patients at the time of the 120-day safety update and for assessment by the Advisory Committee.

Several formal meetings also occurred between the sponsor and FDA to discuss manufacturing changes. Vedolizumab was initially manufactured utilizing a mouse myeloma (NS0) cell line, and initial clinical studies used drug product from this process (MLN02, Process A). A Chinese hamster ovary (CHO) cell line was developed to improve productivity, and drug product from this process (MLN0002, Process B) was used in multiple Phase 1 and 2 clinical studies. Further manufacturing improvements to the CHO-based process were then implemented to establish a commercially representative process (MLN0002, Process C) that was used to supply Phase 3 clinical trials. A PK/PD comparability study was completed prior to initiating Phase 3 studies, to compare Process B and C products. For simplicity, “vedolizumab” will be used throughout this review to refer to the drug product throughout its development.

Presubmission regulatory activities related to this submission included an advisory committee meeting and 14 formal face-to-face meetings between the sponsor and FDA. In addition, there were a number of teleconferences and written correspondences exchanged during the development program for ulcerative colitis. The sponsor was granted Fast Track Designation in February 2013. Table 2 below summarizes pre-submission regulatory meetings and submissions and highlights key clinical agreements. A more detailed account of formal meetings and agreements is provided in Appendix 1.

Table 2: Pre-submission Regulatory History for BLA 125476

Date	Regulatory Action(s)
June 7, 2000	Original IND 9125 submitted for MLN02
June 2004	Type C Meeting to discuss the clinical development outcomes from two Phase 2 studies, M200-021 and L299-016.
January 24, 2006	IND 9125 placed on clinical hold for insufficient information to allow the Agency to assess the risk of progressive multifocal leukoencephalopathy (PML) to subjects with MLN02
April 4, 2006	Type A Meeting to discuss options for removing clinical hold, including PML risk minimization and safety monitoring.
July 26, 2006	Type C Meeting to discuss manufacturing changes from MLN02 to MLN0002
June 18, 2007	Sponsor submitted an amendment which was a complete response to the clinical hold and included the RAMP algorithm for PML risk minimization and monitoring.
July19, 2007	Removal of clinical hold based on additional safety measures related to potential PML risk
December 11, 2007	Type C Meeting to continue discussions about PML risk management program
April 18, 2008	Type C meeting to discuss overall development plan for MLN0002, specifically dose selection, CMC, and nonclinical data to support Phase 3 studies.
June 5, 2008	Type C, End of Phase 2 Meeting to discuss pivotal studies for the proposed IBD indications
September 16, 2008	Type B, End of Phase 2 meeting to discuss the CMC development plan
September 26, 2008	Type C End of Phase 2 Teleconference to discuss outstanding clinical questions and issues for Phase 3 activities
September 10, 2009	Type C, Phase 3 meeting to discuss the Statistical Analysis Plan for the Phase 3 Crohn's disease study, C13007
July 13, 2010	Meeting to discuss Phase 3 development plan
July 20, 2011	Closed Joint Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee
September 6, 2011	Type C follow-up Meeting to discuss the outcomes from the Joint GIDAC/DSaRM meeting
July 24-25, 2012	Type C, post-Phase 3 meeting to discuss pivotal study data and clinical plan to support registration
November 6, 2012	Type C, Pre-BLA meeting to discuss clinical, nonclinical, and regulatory aspects of the BLA
November 13, 2012	Type B, Pre-BLA meeting to discuss CMC aspects of the BLA
February 21, 2013	Fast track designation granted for vedolizumab in the treatment of ulcerative colitis and Crohn's disease

2.6 Other Relevant Background Information

There is no other relevant background information, other than that discussed in other sections of this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity are acceptable. The electronic application was well-organized and easily navigable.

The Office of Scientific Investigations (OSI) is scheduled to perform site investigations of 4 clinical sites:

Table 3 Clinical Site Inspections

Clinical Site Number	Location	Number of Subjects Screened/Randomized/Prematurely Discontinued	Site Selection Rationale
58045	Seattle, WA	24/15/10	Highest US enrollment
58156	San Antonio, TX	10/8/4	High efficacy in Induction and Maintenance Trials
04006	Leuven, Belgium	49/41/25	Highest overall enrollment
12019	Czech Republic	9/9/4	Highest efficacy compared to placebo

Reviewer comment: OSI inspection reports are pending at the time of this review. An addendum will be provided with pertinent information from the OSI report.

3.2 Compliance with Good Clinical Practices

There was a statement of Good Clinical Practice. "Each of the clinical studies was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulatory requirements."

The application also included a debarment certification that the applicant did not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

The sponsor provided a single signed copy of FDA Form 3454 with an appended list of investigator names from each covered study. This certified that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No FDA Form 3455s were provided, as no investigators reported financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Vedolizumab is recombinant humanized IgG_1 monoclonal antibody composed of two light chains of the kappa subclass and two heavy chains linked together by two disulfide bridges to form a Y-shaped molecule.

Figure 1: Schematic diagram of vedolizumab

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Vedolizumab is produced in CHO cells and has a molecular weight of approximately 147 kDa. (b) (4)

[redacted] During product development, several manufacturing changes were implemented. These resulted in 3 different iterations of the product (process A, B, and C). Significant changes included:

- Changing the host cell line from NS0 to CHO to improve productivity and the product quality profile
- [redacted] production scale (commercialization scale)

The impact of these changes was assessed through a variety of biochemical, biophysical, immunological, and pharmacological assessment, and the results support the comparability of vedolizumab across these processes. Process A was [redacted] was studied in phase 1 and phase 2 trials. Process B was [redacted] and process C is a lyophilized formulation for infusion or injection. Bioequivalence between Processes B and C was demonstrated in healthy subjects in Study C13009.

The drug product is a sterile, lyophilized formulation which contains histidine/histidine [redacted] arginine HCl, sucrose, and polysorbate 80. Each single-use vial provides 300mg vedolizumab and is reconstituted with 4.8 mL Sterile Water for Injection. The reconstituted drug product is then diluted into 0.9% sodium chloride to an approximate volume of 250 mL.

There are no major efficacy or safety issues from chemistry, which recommends approval. For more information see the Product Quality Review.

4.2 Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because vedolizumab is not an antimicrobial agent. Drug quality microbiology considerations are below.

At the time of this review, there were still several outstanding drug quality microbiological issues related to this application. Specifically,

(1) Uncertainly about the validity of the endotoxin test methods used to assess endotoxin in the final drug product: The applicant has not determined the effect of spiking endotoxin and holding undiluted formulated drug product on endotoxin recovery over time. Many of the biotech formulations with polysorbate in combination with certain other excipients have been reported to exhibit “Low Endotoxin Recovery” (LER). In the event that spiked endotoxin cannot be

recovered from formulated drug product, a path forward must be found for endotoxin release testing of the drug product.

(2) Rabbit Pyrogen Test: At filing and in an IR submitted 9/26/2013, the applicant was requested to perform and submit the results for rabbit pyrogen testing as described in 21CFR610.13(b). In Amendment 125476.25 Takeda noted that the *July 2012 Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers* states that the requirement in 21CFR610.13(b) may be waived if a method equivalent to the rabbit test is demonstrated as per 21CFR610.9. However, the proposed LAL method has not been demonstrated to be equivalent to the Rabbit Pyrogen Test. In addition, biotech products may contain pyrogens not detected by compendial LAL test methods. The sponsor should perform the Rabbit Pyrogen Test on three batches of finished drug product and submit results to the Agency to ensure that the product does not contain unexpected pyrogens. If the LAL endotoxin release test is valid (see 1 above), the Rabbit Pyrogen Test does not need to be performed on all lots at release.

(3) Inadequate Container Closure Integrity (CCI) Validation. The method sensitivity for CCI validation testing was not stated, and the positive controls used for validation (vials with known perforations), were inadequate.

In addition to the above, the applicant initially proposed in the label a (b) (4) The labeling team has revised this to (b) (4) at 2 – 8°C because (b) (4) has not been provided. This issue was noted in an information request from 9/26/2013. Takeda responded that they would provide the data by the end of 2013. The labeling team may elect to change the label (b) (4) pending receipt of this data.
For more information, see the Quality Microbiology Review by Stephen Fong, PhD.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical assessment of vedolizumab included pharmacology, pharmacokinetics, acute IV toxicology in monkeys, repeated dose IV toxicology in monkeys and rabbits, reproductive toxicology, and local tolerance studies. In addition, special nonclinical studies were completed in order to compare the impact of vedolizumab and natalizumab on immunotoxicity and CNS immune surveillance.

In Vitro Pharmacology

Comparative binding affinity of vedolizumab for the α4β7 integrin was determined in competitive binding assays using peripheral blood lymphocytes of Cynomolgus monkey and human whole blood. These studies demonstrated that the binding affinities of vedolizumab for either B or memory CD4 lymphocytes appeared to be similar in

Cynomolgus monkeys and humans. In vitro studies utilizing human and murine cell lines selectively expressing specific integrins demonstrated the specificity of vedolizumab for binding to the α4β7 integrin and not α4β1 or αEβ7 integrin. The selectivity of vedolizumab for inhibition of α4β7-mediated cell adhesion interactions was also examined and showed that vedolizumab inhibited α4β7-MAdCAM-1 and fibronectin and did not inhibit α4β7-VCAM-1, α4β1-VCAM-1, or α4β1-fibronectin-mediated adhesive interactions.

In vitro studies also demonstrated that vedolizumab did not mediate antibody dependent cell-mediated cytotoxicity or complement dependent cytotoxicity in human peripheral blood mononuclear cells. In addition, vedolizumab did not induce T lymphocyte activation or cytokine release. Tissue cross-reactivity studies were conducted using a panel of monkey and human tissues, and no unanticipated tissue cross reactivity was observed.

In Vivo Pharmacology

An animal efficacy study was conducted in Tamarin monkeys with naturally occurring chronic colitis using ACT-1 (murine homologue of vedolizumab). ACT-1 treatment resulted in resolution of diarrhea in all animals by Day 3 and colonic mucosal biopsies on Day 5 showed ACT-1 localization to the $\alpha4\beta7^+$ lymphocytes in the lamina propria. Biopsy results also revealed reduced mucosal density of $\alpha4\beta7^+$ lymphocytes from Day 5 to Day 20. Control animals had no clinical or immunohistologic improvement.

Toxicology

Toxicity studies were conducted in Cynomolgus monkeys. Lymphoplasmacytic gastritis was observed in both MLN0002 and control monkeys in a 26-week study, though MLN0002 treated monkeys had greater regeneration of superficial mucosal epithelium in response to this gastritis. The significance of this is not known. *Balantidium coli* (parasites) were observed in the cecum and colon of both control and vedolizumab treated monkeys, and no dose response in vedolizumab treated monkeys was observed.

In a 3-month toxicity study of New Zealand white rabbits, no differences were noted between control animals and those treated with vedolizumab. A reproduction study in pregnant New Zealand white rabbits showed no evidence of impaired fertility or harm to the fetus with vedolizumab administration on gestation day 7 at single IV doses up to 100 mg/kg. Similarly, a pre and postnatal development study with vedolizumab in monkeys showed no evidence of any adverse effect on pre and postnatal development at IV doses up to 100 mg/kg.

Special Nonclinical Studies

A decrease in immune surveillance of the CNS by T-lymphocytes is hypothesized to contribute to the development of PML. The sponsor conducted a study using an Experimental Autoimmune Encephalomyelitis (EAE) model in Rhesus monkeys (a model of multiple sclerosis; there is no animal model of PML) to assess the impact of vedolizumab and natalizumab on CNS immune surveillance. The results of this study showed that while natalizumab appeared to inhibit immune surveillance of the CNS, vedolizumab had no such effect.

In addition, a 3-week comparative immunotoxicity study of natalizumab and vedolizumab was completed in Cynomolgus monkeys. Natalizumab caused a significant increase in lymphocyte populations (e.g., b-lymphocytes, t-helper lymphocytes, etc.), whereas there was no change in these populations in vedolizumab-treated monkeys.

There are no major efficacy or safety issues from nonclinical, which recommends approval. For more information see the Nonclinical Review by Tamal Chakraborti.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team found the information submitted to support this BLA to be acceptable with the following recommendations for post marketing commitment (PMC) studies:

- A study to reanalyze banked immunogenicity serum samples from ulcerative colitis trial C13006 and Crohn's disease trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference. This recommendation is based on the finding of inadequate assessment of immunogenicity incidence in the current BLA.
- Evaluate the disease-drug-drug interaction (DDDI) potential between vedolizumab and other CYP substrates. This recommendation is based on the current understanding that CYP enzymes expression is suppressed by inflammatory cytokines associated with inflammatory conditions, and they can normalize upon improvement of the inflammatory conditions. We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of UC or CD, an inflammatory disease condition, on the exposure of CYP substrate drugs (i.e., the disease drug interaction). Such study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the DDDI.

Additional summary information from the clinical pharmacology review is provided below. For more detailed information see the Clinical Pharmacology Review by Lanyan Fang, PhD, Yow-Ming Wang, PhD, Justin Earp, PhD, Nitin Mehrotra PhD, Sarah Dorff, PhD, and Michael Pacanowski, PharmD.

4.4.1 Mechanism of Action

Vedolizumab is a recombinant humanized IgG1 antibody which selectively binds α4β7 integrin, a glycoprotein on the surface of leukocytes which are involved in GI mucosal immunity. Vedolizumab blocks the interaction of human lymphocyte integrin α4β7 with its ligand, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of intestinal vasculature. This inhibits the migration of these leukocytes into the GI mucosa and thus decreases the inflammation associated with UC.

4.4.2 Pharmacodynamics

Study C13002 assessed the relationship between vedolizumab serum concentrations and the extent of α4β7 binding saturation in three dose cohorts (2, 6, and 10 mg/kg). Subjects received a total of 4 vedolizumab doses administered at Days 1, 14, 29, and 85. Maximum binding saturation (i.e., near 100% inhibition of MAdCAM-1-Fc binding to α4β7) occurred within one hour of vedolizumab administration at all dose levels, suggesting that maximum inhibition of α4β7 is unrelated to dose. Maximum inhibition persisted throughout treatment until 84, 126, and 112 days after the last dose for the 2, 6, and 10 mg/kg dose cohorts, respectively. The significance of the saturation of the α4β7 receptor is only one factor related to drug efficacy. These results suggest that near-maximum α4β7 binding will be maintained with the recommended dosing regimen of 300 mg Q8W.

4.4.3 Pharmacokinetics

Vedolizumab exhibits target-mediated drug disposition leading to decreased clearance with increasing doses, due to target saturation. However, the exposure was approximately dose-proportional over the dose range of 2 to 10 mg/kg, following repeated dose administration in UC patients. The mean apparent terminal half-life was approximately 25 days at 300 mg dose. The population PK analysis showed disease severity, body weight, serum albumin, age, prior TNFα antagonist therapy, and concomitant medications had no clinically meaningful impact on PK.

The clinical pharmacology assessment found the proposed dosing regimen (i.e., 300 mg at Weeks 0, 2, 6 and Q8W thereafter) acceptable based on exposure response data. The exposure response analysis in Study C13006 was based on the ITT population, where the trough concentration was used as the exposure variable and

clinical remission at both Weeks 6 and 52 was used as the primary response variable. A significant relationship was established between clinical remission at Week 6 and vedolizumab Week 6 trough concentration using logistic relationship. This may suggest that higher exposures is associated with higher efficacy, however, the clinical pharmacology reviewer suggests that the exposure-response relationships are confounded by several risk factors (e.g., TNFα antagonist use, concomitant medications) which are not well balanced across the concentration quartiles at Week 6. No exposure-response relationships were evident between clinical remission at Week 52 and vedolizumab trough concentrations. This is consistent with the lack of dose-response observed between the Q4W and Q8W dosing regimens at Week 52.

4.4.4 Immunogenicity

The immunogenicity of vedolizumab could not be reliably assessed during clinical development due to drug interference in the immunogenicity assay. The drug tolerance level of the immunogenicity assay (500 ng/mL) was significantly less than the mean vedolizumab steady state trough concentrations during clinical trials, so the incidence of ADA were likely to be underestimated during treatment. For example, 4% of patients who received continuous vedolizumab in Studies C13006 and C13007 developed anti-drug antibodies at any time during treatment; however, 17% of patients who received vedolizumab during induction but placebo during the maintenance phase had ADAs at Week 52, when drug levels were undetectable. Since ADAs could degrade during this time period, 17% may still be an underestimation of the true immunogenicity rate. There were 8 patients with persistently positive ADA, and none of these patients achieved clinical remission at Weeks 6 or 52 in controlled trials. Seven of these subjects had available drug concentration data which showed undetectable vedolizumab concentrations in 5 patients and reduced vedolizumab concentrations in 2 patients.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4. Overview of Clinical Development Program Supporting Efficacy for Ulcerative Colitis

Study ID	Study Design	Study Population	Treatment Arms	Study Enrollment	Primary Endpoint	Relevant Efficacy Endpoints
C13002	Phase 2, randomized, double-blind, placebo-controlled PK/PD, multiple dose	Male or female, aged 18 – 70, with active UC (Mayo score of 1 to 7)	2.0 mg/kg, 6.0 mg/kg, 10.0 mg/kg, or placebo on Days 1, 15, 29, and 85	VDZ: 38 Placebo: 9	Safety, tolerability, PK, and PD of multiple doses of VDZ	- changes in UC activity based on partial Mayo score (exploratory efficacy analysis)
M200-022	Phase 2, randomized, double blind, placebo-controlled, dose-response, parallel group study of efficacy and safety	Male or female, aged 18-80, with active UC, not receiving corticosteroids of immunosuppressive agents	0.5 mg/kg, 2.0 mg/kg, or placebo on days 1 and 29	VDZ: 118 Placebo: 63	Clinical remission[a] (Day 43)	- time to failure - time to relapse - change over time in mean UCCS, modified Baron Score, Powell Tuck score, IBDQ score, serum CRP concentrations, and Riley histopathological score
C13006	Phase 3, randomized, placebo-controlled, double-blind, multicenter study	Male or female, aged 18 – 80, with moderately to severely active UC and inadequate response to, loss of response to, or intolerance of 1 or more of the following therapies: immunomodulators, corticosteroids[b], or TNFα antagonists.	300 mg or placebo at Weeks 0 and 2	VDZ: 225 Placebo: 149	Clinical Response (Week 6)	- clinical remission (6 wks) - mucosal healing (6 wks)
			300 mg Q4W or Q8W or placebo from week 6 until week 52	VDZ Q4W: 125 VDZ Q8W: 122 Placebo: 126	Clinical Remission (Week 52)	- durability of clinical response - mucosal healing (52 wks) - durability of clinical remission - corticosteroid free remission (52 wks)
C13008	Phase 3, open-label, long-term, safety extension study with exploratory efficacy endpoints	Male or female, aged 18 – 80, rolling over from previous qualifying VDZ studies. De novo patients were also enrolled but only included in safety analyses.	300 mg Q4W	Total: 2243 UC VDZ Patients: 894	Safety of long-term VDZ treatment (AEs, vitals, labs, ECGs)	- changes in UC activity based on partial Mayo scores (exploratory efficacy analysis) - time to major IBD-related events (hospitalizations, surgeries, or procedures) - changes from baseline in IBDQ, SF-36, and EQ-5D scores
C13004	Phase 2, multiple-dose, open-label, multicenter, long-term safety study w/ exploratory efficacy endpoints	Male or female, aged 18 – 75, with active UC or CD. Study included de novo UC or CD patients, as well as UC rollover patients from C13002.	2.0 mg/kg or 6.0 mg/kg loading doses on Days 1, 15, and 43 followed by Q8W for up to 78 weeks	Total: 72 UC VDZ patients: 53	Long-term safety of VDZ treatment	- change over time in partial Mayo scores, IBDQ scores, and serum CRP concentrations (exploratory efficacy analyses)

[a] Clinical remission in M200-022 was defined as a 0 or 1 in the total UCCS and 0 to 1 in the modified Baron score with no evidence of rectal bleeding at the Day 43 evaluation
[b] failure of corticosteroids alone was sufficient for inclusion outside the US only

5.2 Review Strategy

For this BLA submission, Clinical Trial C13006 was reviewed in detail. Details of the study design and conduct are contained in Section 5 and at times are separated into

C13006 Induction Phase/Study and C13006 Maintenance Phase/Study. Study results are discussed in Sections 6 (efficacy) and 7 (safety).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title
Study C13006
A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis

Study Centers
This study was conducted in 34 countries at 211 centers. The participating countries are listed in Table 5 below.

Table 5: Study Centers by Country

Location	Number of Centers	Number of Patients
United States	**63**	**238**
Outside the US	**148**	**657**
Canada	16	92
Australia	13	53
India	13	58
Germany	7	17
Poland	7	60
Russia	7	49
South Africa	7	19
South Korea	7	41
Belgium	6	56
Czech Republic	6	38
Italy	6	21
France	5	17
Hungary	5	16
Austria	4	19
Malaysia	4	9
Norway	4	9
Denmark	3	14
Greece	3	5
Estonia	2	10
Iceland	2	3
Israel	2	2
New Zealand	2	11
Netherlands	2	3
Spain	2	2
Switzerland	2	6
Taiwan	2	3
Turkey	2	6
United Kingdom	2	6
Bulgaria	1	6
Hong Kong	1	1
Ireland	1	1
Latvia	1	3
Singapore	1	1

Study Objectives

Primary Objective Induction Phase:

- To determine the effect of vedolizumab induction treatment on clinical response in patients with moderately to severely active UC at 6 weeks.

Primary Objective Maintenance Phase:

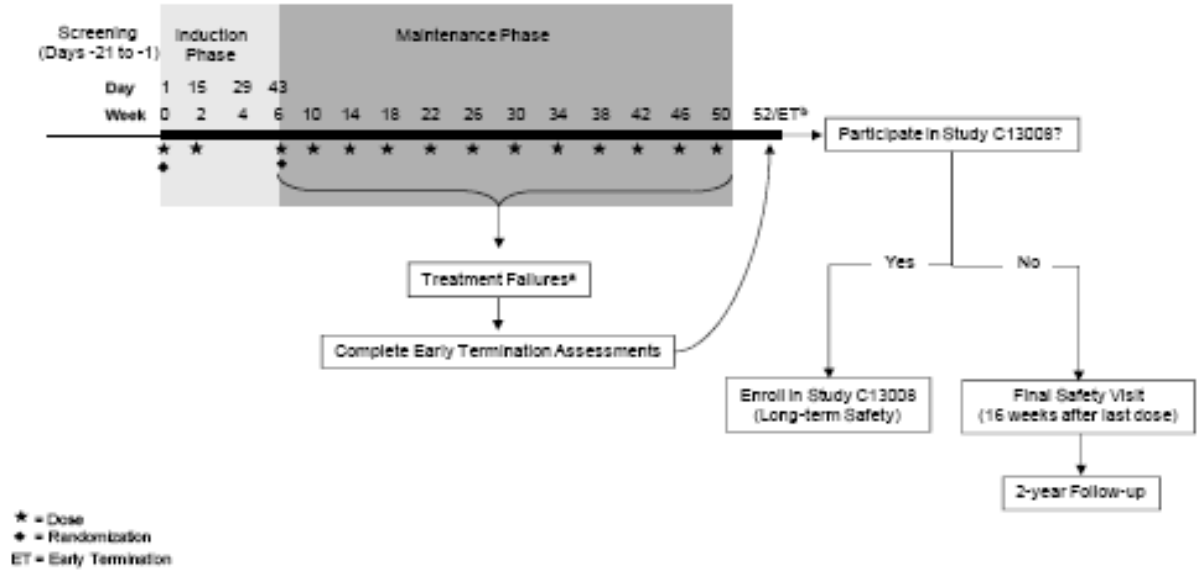
- To determine the effect of vedolizumab maintenance treatment on clinical remission in patients with moderately to severely active UC at 52 weeks.

Study Design

Trial C13006 was a Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of both induction and maintenance treatment with vedolizumab in 895 patients with moderately to severely active UC. This trial was conducted under a single protocol but designed and analyzed as 2 separate studies: C13006 Induction Study and C13006 Maintenance Study.

The overall study consisted of a 6-week Induction Phase which included study drug dosing at weeks 0 and 2 and endpoint assessments at Week 6 followed by a Maintenance Phase which began with study drug dosing at Week 6 and concluded with Week 52 assessments[1]. Patients who completed through Week 52 or withdrew early due to sustained nonresponse, disease worsening, or the need for rescue medications were eligible to enroll in an open label extension study, Study C13008. Those not participating in Study C13008 were to complete a final safety visit 16 weeks after the last dose of study drug and participate in a 2-year follow-up survey.

Figure 2: Clinical Study Design



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[1] The terms Induction Phase and Maintenance Phase refer to operational aspects of the study and include patients who are not part of the randomized studies (i.e., patients receiving open-label vedolizumab). The terms Induction Study and Maintenance Study specifically refer to the placebo-controlled formal efficacy analyses of vedolizumab administered as induction or maintenance therapy, respectively.

The 6-week Induction Phase consisted of two cohorts of patients. Cohort 1 patients determined to be eligible at screening were randomized 3:2 to treatment with double-blind vedolizumab 300mg IV or placebo, at Weeks 0 and 2. Randomization was stratified for two factors:

- concomitant use of oral corticosteroids
- previous exposure to TNFα antagonists or concomitant immunomodulator (6-mercaptopurine or azathioprine) use.

The efficacy analyses of vedolizumab for the Induction Study include data from Cohort 1 only. After enrollment in Cohort 1 was complete, patients were enrolled into Cohort 2 to ensure that the sample size of induction responders would be sufficient to power the Maintenance Study efficacy endpoints. Patients in Cohort 2 received open label vedolizumab 300mg IV at weeks 0 and 2 and were assessed at Week 6 to determine if they were eligible for the Maintenance Study.

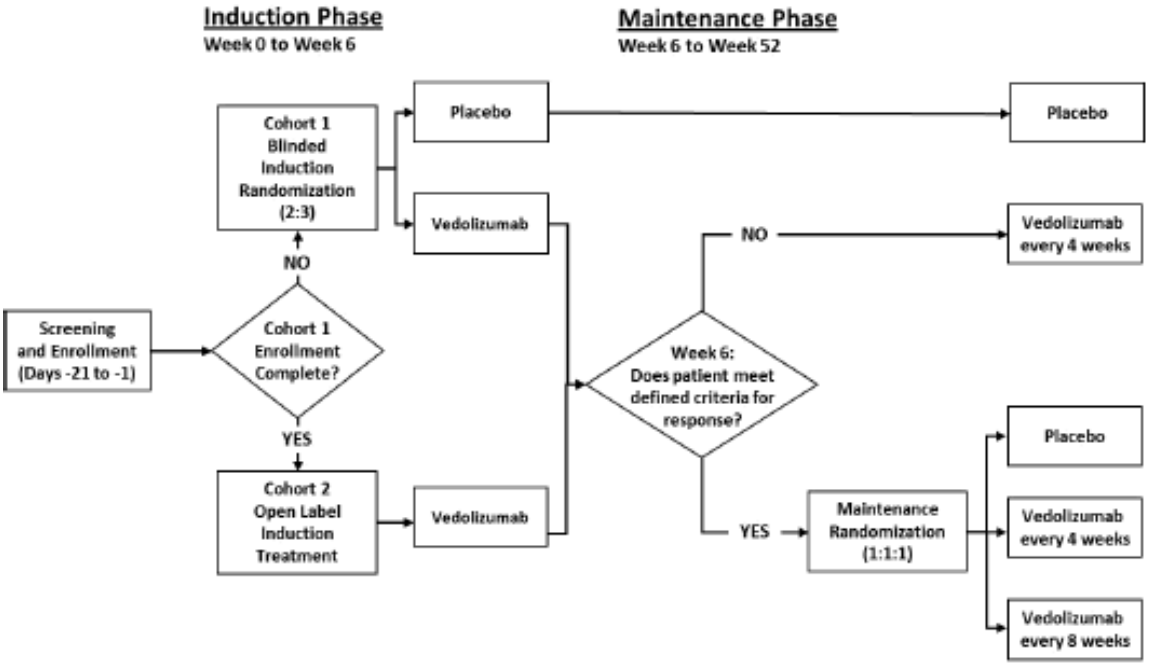
All patients from the Induction Phase continue on to the Maintenance Phase and were included in the maintenance safety database. Patients from both Induction cohorts who received vedolizumab and achieved clinical response at Week 6 were randomized in a 1:1:1 ratio to double-blind treatment with vedolizumab every 4 weeks (Q4W), vedolizumab every 8 weeks (Q8W), or placebo. Randomization was stratified for three factors:

- enrollment in Cohort 1 or 2 of the Induction Phase
- concomitant use of oral corticosteroids
- previous exposure to TNFα antagonists or concomitant immunomodulator (6-mercaptopurine or azathioprine) use.

The Maintenance Study efficacy analyses include data from these randomized patients only.

Vedolizumab-treated patients who did not demonstrate response at Week 6 of the Induction Phase continued with vedolizumab infusions every 4 weeks through Week 52 and were included in exploratory analyses evaluating delayed clinical response at Weeks 10 and 14, as well as safety assessments. In addition, patients who received double-blind placebo during the Induction Phase continued on placebo infusions every 4 weeks during the Maintenance Phase, regardless of treatment response, and were included in the safety assessments. Data from all patients were included in the safety analysis. Figure 3 shows the overall trial design of C13006.

Figure 3: Overall Trial Design



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Reviewer comment: Rerandomization of responders at Week 6 allows a separate analysis of maintenance of clinical remission.

5.3.2 Key Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study.

1. Age 18 to 80

2. Male or female who is voluntarily able to give informed consent

3. a. Female patients who are at least 1 year post-menopausal or surgically sterile or agree to practice 2 effective methods or contraception or completely abstain from heterosexual intercourse

   b. Male patients who agree to practice effective barrier contraception through 6 months after the last dose of study drug or completely abstain from heterosexual intercourse

4. Diagnosis of UC established at least 6 months prior to enrollment by clinical and endoscopic evidence and histopathology report

5. Moderately to severely active UC as determined by a Mayo score of 6 to 12 with an endoscopic subscore ≥ 2 within 7 days prior to the first dose of study drug

6. Evidence of UC extending proximal to the rectum (≥ 15 cm of involved colon)

7. Patients with extensive colitis or pancolitis of > 8 years duration or left-sided colitis of > 12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (may be performed during screening)

8. Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factor must be up to date on colorectal cancer surveillance (may be performed during screening)

9. Demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:
    a. Immunomodulators
        i. Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-mercaptopurine (≥ 0.75 mg/kg) ***OR***
        ii. History of intolerance of at least 1 immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, *TPMT* genetic mutation, infection)
    b. TNFα antagonists
        i. Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of infliximab 5 mg/kg IV, 2 doses at least 2 weeks apart ***OR***
        ii. Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) ***OR***
        iii. History of intolerance of infliximab (including but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)
    c. Corticosteroids – this is only applicable to patients outside the US
        i. Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or IV for 1 week, ***OR***
        ii. Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions, ***OR***

iii. *History of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection).*

10. May be receiving a therapeutic dose of the following drugs:
    a. Oral 5-ASAs compounds provided that the dose has been stable for the 2 weeks immediately prior to enrollment
    b. Oral corticosteroid therapy (prednisone at a stable dose ≤30 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to enrollment if corticosteroids have just been initiated, or for the 2 weeks immediately prior to enrollment if corticosteroids are being tapered
    c. Probiotics (e.g., Culturelle, Saccharomyces boulardii) provided that the dose has been stable for the 2 weeks immediately prior to enrollment
    d. Antidiarrheals (e.g., loperamide, diphenoxylate with atropine) for control of chronic diarrhea
    e. Azathioprine or 6-mercaptopurine, provided that the dose has been stable for the 8 weeks immediately prior to enrollment (for patients participating in the US, these medications were allowed only for those in Cohort 1)

Reviewer comment: The US and ex-US populations differ in their allowance of patients in the trial who failed corticosteroids only. This has the potential to affect the results, as corticosteroid only failures may have less serious disease. In addition, the applicant includes patients with intolerance to TNFα (including but not limited to infusion-related reaction, demyelination, congestive heart failure, infection) as TNF failures, however, this reviewer questions some of the criteria included under intolerance and believes it may be more appropriate to consider only those patients who failed to respond or lost response after treatment in this subgroup, as the criteria for intolerance are more ambiguous. This is discussed further in Section 6.1.4.

5.3.3 Key Exclusion Criteria

The exclusion criteria are identical for both the Induction Study and Maintenance Study portions of C13006

1. Gastrointestinal Exclusion Criteria
    a. Evidence of abdominal abscess or toxic megacolon
    b. Extensive colonic resection, subtotal or total colectomy
    c. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
    d. Within 30 days prior to enrollment, have received any investigational or approved non-biologic therapies (other than those listed in the inclusion criteria above), for the treatment of underlying disease
    e. Within 60 days prior to enrollment, have received infliximab or any other investigational or approved biologic agent

f. Any prior exposure to natalizumab, efalizumab, or rituximab
g. Use of topical 5-ASA or corticosteroid enemas/suppositories within 2 weeks of administration of the first dose of study drug
h. Evidence of or treatment for C difficile infection within 60 days or other intestinal pathogen within 30 days prior to enrollment
i. Currently require or are anticipated to require surgical intervention for UC during the study
j. History or evidence of adenomatous colonic polyps that have not been removed
k. History or evidence of colonic mucosal dysplasia
l. Diagnosis of Crohn's disease or indeterminate colitis

2. Infectious disease exclusion criteria
    a. Chronic hepatitis B or hepatitis C infection
    b. Active or latent TB
    c. Any identified congenital or acquired immunodeficiency
    d. Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine
    e. Clinically significant extra-intestinal infection within 30 days prior to enrollment
3. general exclusion criteria
    a. Previous exposure to vedolizumab
    b. Female patients who are lactating or have positive pregnancy test
    c. Unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
    d. Any surgical procedure requiring general anesthesia within 30 days prior to enrollment, or planning surgery during study period
    e. Any history of malignancy, except for adequately treated nonmetastatic basal cell skin cancer, squamous cell skin cancer that has not recurred for at least 1 year prior to enrollment, and history of adequately treated cervical carcinoma in situ that has not recurred at least 3 years prior to enrollment
    f. History of any major neurological disorders
    g. Positive PML subjective symptom checklist
    h. Lab abnormalities during the screening period, specifically: hemoglobin, WBC count, lymphocyte count, platelet count, ALT, AST, alkaline phosphatase, serum creatinine
    i. Current or recent history of alcohol dependence or illicit drug use
    j. Active psychiatric problems that may interfere with compliance
    k. Unable to attend all study visits or comply with procedures

Reviewer comment: *The exclusion criteria are appropriate for the trial.*

5.3.4 Treatment

Patients received vedolizumab or placebo by IV infusion according to their treatment assignment. All infusions were to be administered IV over approximately 30 minutes under the supervision of the investigator or identified designee(s). Longer infusion times of up to 60 minutes were permitted in individual patients based on intolerance to shorter infusion times. Patients were to be observed for 2 hours post-infusion of the first dose and 1 hour after completion of subsequent doses.

Induction Phase:

- Intention to treat population: Patients randomized to vedolizumab were to receive vedolizumab 300 mg at Weeks 0 and 2. Patients randomized to placebo were to receive 250 mL of 0.9% sodium chloride IV at Weeks 0 and 2.
- Cohort 2: All patients from Cohort 2 were to receive open-label vedolizumab 300 mg at Weeks 0 and 2.

Maintenance Phase:

- Intention to treat population:
  - There were 2 vedolizumab dosing groups: the Q4W patients received vedolizumab 300mg infusions every 4 weeks from week 6 to week 50, and the Q8W patients received vedolizumab 300 mg every 8 weeks at Weeks 6, 14, 22, 30, 38, and 46 and placebo saline infusions at Weeks 10, 18, 26, 34, 42, and 50, to maintain blinding.
  - patients randomized to the placebo group were to receive 250 mL of 0.9% sodium chloride IV every 4 weeks from Week 6 through Week 50.
- Induction Phase non-responders: Pts. who received vedolizumab and failed to respond at Week 6 received open-label vedolizumab infusions every 4 weeks from Week 6 through Week 50.
- Placebo group: Patients assigned to the placebo group in the Induction Phase continued double-blind IV saline infusions every 4 weeks from Week 6 through Week 50.

Reviewer comment: Infusion reactions could have the potential to affect the blinding if they occurred disproportionately in the vedolizumab treatment groups, however, investigator-defined infusion-related events were uncommon in Study C13006. Infusion events did occur more frequently in vedolizumab treated patients (5% of combined vedolizumab patients vs 1% of placebo), but this reviewer believes given the low numbers this will not impact the efficacy results. This is discussed further in Section 7.3.5, Submission-Specific Primary Safety Concerns.

5.3.5 Study Visits and Procedures

Induction Phase

The induction Phase included a screening period, induction treatment, and observation period. The schedule of events and study procedures for the Induction Phase are included in Table 6 below.

Table 6: Induction Phase Schedule of Events

Study Procedures [a]	Screening	Induction Treatment		Observation	
	Days -21 to -1	Week 0/Day 1	Week 2/ Day 15 (± 2 days)	Week 4/ Day 29 (± 2 days)	Week 6 [c]/ Day 43 (± 2 days)
Informed consent, wallet card, demographics, medical history, prior therapies, UC history	X				
Physical examination	X	X	X		X
Neurological examination	X				X
Vital signs	X	X	X	X	X
PML checklist	X		X		X
Diary instruction	X				
Diary review [b]		X	X	X	X
Concomitant medications or procedures	X	X	X	X	X
Randomization/treatment assignment		X			
Dosing		X	X		
Complete Mayo score [b]	X				X
Partial Mayo score		X	X	X	
IBDQ, SF-36, EQ-5D	X				X
Stool sample	X				
12-lead ECG	X				X
TB screening, CXR	X				
AEs [d]	X	X	X	X	X
Sample collection for:					
Pregnancy test [e]	X	X	X		X
HBV, HCV, HIV	X				
JCV DNA	X				X
Genomic DNA		X			
Clinical chemistry, hematology [f]	X	X	X	X	X
Coagulation	X				X
Urinalysis	X	X			X
Serum biomarkers		X			X
PD assessment [g]		X			X
Predose PK assessment [g]		X	X		X
Postdose PK assessment [h]		X	X		
HAHA assessment		X			X
Flexible sigmoidoscopy [b]	X				X
Fecal calprotectin	X				X

Source: Clinical Study Report Study C13006, pages 37-38

[a] Patients discontinued from the study for any reason were to complete an Early Termination visit and Final Safety visit. Patients may also be seen for unscheduled visits for disease exacerbation.

[b] Must have occurred within 7 days prior to enrollment with enrollment defined as the point in time at which the patient was assigned a treatment in the Induction Phase

[c] At Week 6, patients entered the Maintenance Phase. The procedures in this table were to be performed prior to receiving the Week 6 dose.

[d] Collection of SAE's began once informed consent was signed and non-serious AEs began following the first administration of study drug on Day 1. Collection continued through Week 66/final safety visit, or until enrollment in Study C13008.

[e] All females must have serum pregnancy test at screening and a completed urine pregnancy test prior to each dose of study drug.
[f] Labs taken on days where patient was dosed with study drug were to be drawn prior to dosing. Pharmacodynamic sampling was for US patients only, as it was determined that this would provide sufficient samples to evaluate the PD of vedolizumab.
[g] Predose PK, PD (US patients only), and HAHA samples were to be obtained within 30 minutes prior to dosing.
[h] Postdose PK samples were to be obtained as close to the end of infusion as feasible and must have been within 2 hours after the start of the infusion.

Maintenance Phase

The Maintenance Phase included the maintenance treatment phase and end of study efficacy and safety assessments. The schedule of events and study procedures for the Maintenance Phase are included in Table 7 below.

Table 7: Maintenance Phase Schedule of Events

Study Procedures [b]	Maintenance Treatment												End of Study [a]	
	Week 6 Day 43 (± 3 wks)	Weeks (± 1 wk)											Week 52/ ET (± 1 wk)	Week 66/ Safety visit (± 2 wks)
		10	14	18	22	26	30	34	38	42	46	50		
Physical and neurological examination					X				X				X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist		X	X	X	X	X	X	X	X	X	X	X	X	X
Diary review		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications and procedures		X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization/ treatment assignment	X													
Dosing	X	X	X	X	X	X	X	X	X	X	X	X		
Complete Mayo score													X	
Partial Mayo score		X	X	X	X	X	X	X	X	X	X	X		
IBDQ, SF-36, EQ-5D							X						X	
12-lead ECG													X	X
AE's	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample collection for:														
Pregnancy test [c,d]		X	X	X	X	X	X	X	X	X	X	X	X	X
JCV DNA [c]			X		X		X		X		X		X	
Clinical chemistry and hematology [c]			X		X		X		X		X		X	X
Coagulation [c]						X								
Urinalysis					X				X				X	
Serum biomarkers [c]													X	
PD assessment (US only)													X	
Predose PK [e]			X		X				X		X			
Postdose PK [f]	X				X						X			
HAHA assessment			X			X			X				X	X
Flexible sigmoidoscopy													X	
Fecal calprotectin								X					X	

Source: Clinical Study Report C13006, pp 39-40

[a] After the Week 52/ET visit assessments were completed, patients may have been eligible for Study C13008 (Long-term Safety). All patients who did not enroll into Study C13008 must have completed the Week 66/Final Safety visit. These patients were also to complete a 2-year follow-up survey.

[b] Patients discontinued from the study for any reason were to have completed the ET visit. Patients who did not enroll into Study C13008 must have completed the Week 66/Final Safety visit. These patients were also to complete a 2-year follow-up survey

[c] To be performed prior to dosing

[d] A urine pregnancy test was to be completed for all females prior to each dose of study drug. All females were to have a serum pregnancy test during screening and at Weeks 52 (or ET visit) and 66 (or Final Safety visit).
[e] Predose PK and HAHA samples were to be obtained within 30 minutes prior to dosing.
[f] Postdose PK samples should have been obtained as close to the end of infusion as feasible and must have been within 2 hours after the start of the infusion.

In addition, at any unscheduled visits for exacerbation of UC, the following study procedures were to be performed:

- physical examination, vital signs, diary review, review of concomitant medications and procedures, partial Mayo score, assessment of AEs and SAEs, clinical chemistry, hematology, PK assessment, and HAHA assessment.

Reviewer comments: The schedule of events/assessments was appropriate. Patients who discontinued early from the study for any reason completed an Early Termination visit, Week 66 Final Safety visit, and 2-year follow-up survey. This is important, given the potential for adverse events which may present late in a drug with a long half-life (~25 days) and the risk for PML with similar agents.

5.3.6 Control Procedures

Randomization

Randomization was via a central randomization interactive voice response system (IVRS). Randomized patients received a unique randomization number, and the IVRS provided treatment assignment based on the IVRS. The treatment assignment was obtained from the IVRS by the unblinded site pharmacist who prepared study drug and provided it in masked infusion bags. The randomization process was similar for the Induction Phase and Maintenance Phase.

In the Induction Study, randomization was stratified by:

- concomitant use of oral corticosteroids
- previous exposure to anti-TNF or concomitant immunomodulator use.

In the Maintenance Study, randomization was stratified by

- Induction Phase cohort (Cohort 1 or Cohort 2)
- concomitant use of oral corticosteroids
- previous exposure to anti-TNF or concomitant immunomodulator use

Placebo Control

This was a placebo-controlled trial. In the Induction Phase, patients randomized to placebo received 250 mL of 0.9% sodium chloride by infusion at Weeks 0 and 2. In the Maintenance Phase, patients randomized to placebo received 250 mL of 0.9% sodium

chloride by infusion every 4 weeks from Week 6 to Week 50, and patients randomized to the Q8W vedolizumab group received 250 mL of 0.9% sodium chloride by infusion on visits at which active study drug was not administered, in order to maintain blinding.

Blinding

This was a double-blind trial. All patients, study site personnel (except those involved in drug preparation), and all study personnel involved in the direct operation and execution of the trial were blinded to study drug assignments.

For both vedolizumab and placebo infusions, an unblinded site pharmacist or designee obtained treatment assignments through the IVRS and masked the IV bags after preparation to maintain the study blind. Records of the patient number, the date study drug was dispensed, and the study drug/cohort assignment were maintained by the unblinded pharmacist.

Data Management

Study data were entered from the source documents into eCRFs by site staff. The eCRFs included automated validation checks, and contract clinical research associates performed regular investigative site monitoring visits which included verification of information recorded on eCRFs against source documents. Millennium staff further reviewed the data for completeness and logical consistency.

Reviewer Comments: The applicant utilized adequate control procedures. Infusion reactions occurred at a low rate, though there were more reported in the vedolizumab treated patients than in those receiving placebo (5% combined vedolizumab vs <1% non-ITT placebo, see section 7.3.5 for additional information). This could have had an impact on blinding in these patients.

5.3.7 Primary Efficacy Endpoint

C13006 Induction Study:

- The proportion of patients who achieved a clinical response at Week 6.

C13006 Maintenance Study:

- The proportion of patients who achieved clinical remission at Week 52.

5.3.8 Secondary Efficacy Endpoints

The secondary endpoints are listed below in the order in which they were tested. This is further described in Section 5.3.9, Statistical Information.

C13006 Induction Study:

- The proportion of patients who achieved clinical remission at Week 6.
- The proportion of patients with mucosal healing at Week 6.

C13006 Maintenance Study:

- The proportion of patients with a durable clinical response
- The proportion of patients with mucosal healing at Week 52
- The proportion of patients with durable clinical remission
- The proportion of patients achieving corticosteroid free clinical remission

Primary and secondary efficacy assessments for the Induction and Maintenance Studies were based on Mayo scores. The baseline complete Mayo score was obtained during screening, using patient diary entries within 10 days of enrollment and flexible sigmoidoscopy results within 7 days. The baseline complete Mayo was used for comparison with Week 6 and Week 52 complete Mayo scores, to determine clinical response and remission. The key study endpoint definitions are provided in Table 8, below:

Table 8: C13006 study endpoint definitions

Endpoint	Definition
Clinical Remission	A complete Mayo score of ≤ 2 points and no individual subscore ≥ 1 point
Clinical Response	A reduction in complete Mayo score of ≥3 points and ≥30% from baseline (or a partial Mayo score of ≥2 points and ≥25% from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
Corticosteroid Free Remission	Clinical remission in patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.
Durable Clinical Remission	Clinical remission at Weeks 6 and 52
Durable Clinical Response	Clinical response at Weeks 6 and 52
Mucosal Healing	Mayo endoscopic subscore of ≤1 point

Source: Clinical Study Protocol C13006

In addition to the primary and secondary endpoints, the applicant analyzed a number of exploratory endpoints. For example, subgroup analyses were completed for key endpoints in the subgroup of patients defined as having failed TNFα antagonist therapy and the subgroups of patients on concomitant therapies. In the maintenance phase, additional exploratory endpoints included time to disease worsening, reduction in fecal calprotectin, reduction in oral corticosteroid use. Serum concentrations of vedolizumab

and $\alpha_4\beta_7$ receptor saturation were evaluated as pharmacokinetic and pharmacodynamic endpoints, respectively, and endpoints focusing on resource utilization and patient-reported outcomes included time to major UC-related event and changes from baseline in IBDQ, SF-36, and EQ-5D scores.

Reviewer Comments: Several of the applicant's definitions for study endpoints vary from the FDA's preferred definition. For example mucosal healing does not include a histological component which the Division believes is necessary to support a labeling claim for mucosal healing. Endoscopy subscore alone can only support a labeling claim for improved endoscopic appearance of the mucosa. The prespecified definition for corticosteroid-free remission does not specify a duration of time for which patients were required to be corticosteroid-free, which the Division feels is important. Finally, the Division is beginning to consider rectal bleeding and endoscopy subscore components of the Mayo as particularly relevant to remission (and perhaps should be zero for remission). The sponsor's clinical remission endpoint was agreed upon by the Division prior to submission, however and has been used for other UC applications in the past. This reviewer finds their endpoint definition for clinical remission acceptable. This is discussed in more detail, including the potential impact on study results, in Sections 6.1.4 and 6.1.5.

5.3.9 Statistical Information

Each study was distinct with respect to patient populations, randomization schemes and stratification factors, efficacy endpoints, and Statistical Analysis Plans. Each study was independently powered, and previous exposure to TNFa was limited to 50% of the overall study population, in order to ensure that efficacy data could be obtained in patients who are naïve to this therapy.

The analyses of induction formally evaluated the safety and efficacy of 300 mg vedolizumab versus placebo as an induction therapy. The sample size for the Induction Study was calculated using the assumption that 35% of subjects in the placebo group would achieve clinical response at Week 6. Using this assumption, a total sample size of 375 patients (150 placebo, 225 vedolizumab) would be adequate to detect an 18% difference with 93% power at a 5% significance level.

The analyses of maintenance formally evaluated the safety and efficacy of 300 mg vedolizumab every 4 weeks versus placebo and every 8 weeks versus placebo as maintenance therapy. The sample size calculation for the Maintenance Study was based on the number of patients who received vedolizumab in either Cohort 1 or 2 in the Induction Phase and achieved clinical response by Week 6, based on the prespecified definition for clinical response. Using an assumption that 30% of patients would achieve clinical remission at Week 52, a total sample size of 372 patients (124

per arm) would be adequate to detect a 20% difference with 90% power at a 5% two-sided significance level.

The primary analyses and all proportional-based endpoints (e.g., remission and response) were conducted in the ITT populations. These endpoints were tested using the Cochran-Mantel-Haenszel chi-square test at a 5% significance and were stratified according to:

- Induction Study: concomitant oral corticosteroid use and previous exposure to TNFa antagonists and/or concomitant immunomodulators
- Maintenance Study: enrollment in Cohort 1 or Cohort 2 in the Induction Phase, concomitant oral corticosteroid use, and previous exposure to TNFa antagonists and/or concomitant immunomodulators

Mayo scores and partial Mayo scores for each patient utilized information on stool frequency and rectal bleeding derived from eDiaries completed by the patient for seven days prior to study visits. Subscores were calculated using eDiary information in the following order:

1. The scores from the 3 most recent days prior to the actual day of the study visit will be averaged and rounded to the nearest integer.
2. If the diary entries from 3 days are not available, the scores from the 2 most recent entries will be averaged and rounded to the nearest integer.
3. If less than 2 days of diary data are available, the patient will be categorized as a non-responder and the subscore will be considered missing

All patients who discontinued from the study prematurely for any reason were to be considered as treatment failures for the primary efficacy analyses. Analyses using the PP populations were also provided. The modified ITT populations (defined in Table 9 below) were used for change from baseline analyses, such as analyses of complete Mayo scores. Population definitions are provided in Table 9 below.

Induction Study: The testing of the primary and secondary endpoints was performed using a closed sequential testing procedure to maintain the Type I error rate. The primary induction efficacy endpoint (Clinical Response at Week 6) needed to be significantly different ($p < 0.05$) between vedolizumab and placebo. Provided the primary endpoint was met, each secondary endpoint would be tested using the same closed sequential testing procedure in the following order:

1. clinical remission at Week 6
2. mucosal healing at Week 6

Maintenance Study: In the Maintenance Study, the overall Type I error rate was controlled at a 5% significance level for the 2 comparisons of the primary endpoint of clinical remission at Week 52, using the Hochberg method. If at least 1 of the dosing regimens was significant for the primary efficacy endpoint, the closed sequential testing procedure was used to test significance of the secondary endpoints. The 2

comparisons of the first key secondary endpoint, clinical response at 52 weeks, will be tested at a 5% significance level in the same method as the primary endpoint and controlling for Type I error of the 2 comparisons using the Hochberg method. If at least 1 dose is significant for the first tested secondary endpoint, the two comparisons of the next secondary endpoint (mucosal healing) will be conducted. The order of testing for the secondary endpoints is as follows:

1. durable clinical response
2. mucosal healing at Week 52
3. durable clinical remission
4. corticosteroid free clinical remission

For patients who do not complete the study (because the patient has received rescue medication or discontinued), the last available post baseline measurement (i.e., Last Observation Carried Forward; LOCF) will be used. For the ITT analyses, if there is no post baseline measurement, the baseline measurement will be used.

Table 9: Population Definitions

Population	Definition
Induction Study	
ITT	All randomized patients in Cohort 1 who received any amount of blinded study drug.
m-ITT	All randomized patients in Cohort 1 who received any amount of blinded study drug and had a baseline and at least 1 measurement post-randomization for the endpoint under consideration.

PP	All patients in the ITT population who met the following criteria:
	• Confirmed diagnosis of UC of at least 6 months duration and an enrolling Mayo score between 6 and 12 (inclusive) with an endoscopic subscore of ≥ 2
	• Received the correct study medication as assigned
	• Met 1 or more of the following criteria for treatment failure prior to Day 43:
	  ○ Failed as assessed by the investigator
	  ○ Received any non-study drug due to lack of efficacy
	  ○ Had surgery due to lack of efficacy
	  ○ Had a drug-related AE leading to discontinuation
	• Received both doses of study drug, as assigned
	• Did not receive concomitant corticosteroids or other potentially effective medications (except as permitted per protocol) for an unrelated comorbid condition
	• Had a valid Day 43 assessment (the window for eDiary between 36 and 56 days inclusive and sigmoidoscopy between 29 and 56 days)

Completer (Observed Case)	All ITT-Induction patients who had a baseline (Week 0) and Week 6 assessment for the complete Mayo score.
Safety	All patients in Cohort 1 and 2 who received any amount of study drug in the Induction Phase, according to the actual study drug received.
Maintenance Study	
ITT	All randomized patients who received vedolizumab during the Induction Phase, met the protocol definition for clinical response at Week 6, were randomized in the Maintenance Phase, and received any amount of double-blind study drug in the Maintenance Phase.
m-ITT	All randomized patients who received vedolizumab during the Induction Phase, met the protocol definition for clinical response at Week 6, were randomized in the Maintenance Phase, and received any amount of double-blind study drug and had a baseline and at least 1 post Week 6 measurement in the Maintenance Phase for the endpoint under consideration
PP	All patients in the ITT population who met the following criteria: • Confirmed diagnosis of UC of at least 6 months duration and an enrolling Mayo score between 6 and 12 (inclusive) with an endoscopic subscore of ≥ 2 • Received the correct study medication as assigned

	• Did not have the treatment assignment unblinded by the investigator
	• Met 1 or more of the following criteria for treatment failure prior to Week 52:
	  ○ Failed as assessed by the investigator
	  ○ Received any non-study drug due to lack of efficacy
	  ○ Had surgery due to lack of efficacy
	  ○ Had a drug-related AE leading to discontinuation
	• Received 80% of doses of study drug, as assigned
	• Did not receive concomitant corticosteroids or other potentially effective medications (except as permitted per protocol) for an unrelated comorbid condition
	• Had a valid Week 52 or ET assessment for complete Mayo score

Completers (Observed Case)	All patients from the ITT-Maintenance population who had a baseline (Week 6) and Week 52 assessment for complete Mayo score.
Safety	All patients who received any amount of study drug in the study, according to the actual study drug received.

Reviewer comment: The ITT population included all patients who received a single dose of study drug. The PP population excluded only ITT patients who did not meet certain entry criteria (i.e., Mayo score between 6 and 12 inclusive). There were, therefore, a small number of patients not meeting entry criteria who were included in all analyses populations. This is discussed in more detail in section 6.1.3 below.

The applicant considered a patient a nonresponder based on noncompliance with the eDiary only if they had less than 2 entries from the week prior to study visit. The preferable approach is to consider all patients non-responders if diary entries from 3 days are not available for that patient, however, this was not conveyed to the applicant prior to submission and is not an approval issue. Per the Division's request, the applicant provided a post hoc sensitivity analysis using this preferred approach, and the results were comparable (See Section 6.1.4 below).

5.3.10 Protocol Amendments

The applicant amended the original protocol 4 times, with the first 2 amendments being finalized prior to patient enrollment. The amendments are summarized below:

Amendment 1 (28Oct2008): The washout period for infliximab as well as other biologics was shortened from 90 to 60 days. The applicant's rationale was that a shorter washout period (60 days) was acceptable based on declining drug levels following a minimum of 60 days. The applicant also believed that the change would also minimize the need to

temporize patients with short-term corticosteroids, lessening the possible impact of this on Induction Phase results.

Amendment 2 (28Oct2008): **US amendment only**. Only patients who had previously demonstrated an inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists (but not to corticosteroids) could be included in the study. In addition, US patients who entered the study on concomitant immunomodulators (azathioprine or 6-mercaptopurine) were required to discontinue them at Week 6.

Amendment 3 (02Apr2009): ex-US amendment only. All mechanistic PD objectives, endpoints, and sampling requirements were removed because the anticipated PD sampling in the US was determined to be sufficient.

Amendment 4 (21Apr2009): US amendment only. Collect postdose PK samples as close to the end of infusion as feasible and within 2 hours of the start of infusion, in order to provide adequate data to identify Cmax.

Reviewer Comment: The protocol amendments should not affect the reliability of the study results, however patients enrolled in the US were required to meet more stringent entry criteria and were not allowed concomitant immunosuppressants beyond 6 weeks. Patients meeting US criteria will need to be clearly separated for analyses, in order to best understand the efficacy of the study drug in this population.

6 Review of Efficacy

Efficacy Summary

Clinical Trial C13006 provided statistically persuasive evidence to support that vedolizumab 300mg at Weeks 0, 2, and 6 and every 8 weeks thereafter is effective to support the primary efficacy endpoints:

- Induction of clinical response at Week 6
- Maintenance of clinical remission at Week 52

See also the Risk Benefit Assessment in Section 1.2 above.

6.1 Indication

The Applicant is proposing that vedolizumab receive an indication for reducing signs and symptoms, inducing and maintaining clinical response and remission, and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost

response to, or were intolerant to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist.

6.1.1 Methods

Section 5.3 contains a discussion of the study protocol for Study C13006; Section 6 contains the study results.

6.1.2 Demographics

Induction Phase

The baseline demographics in the induction phase were similar across treatment arms and between Cohorts. Fifty-nine percent (59%) of patients were male and 82% were white. The mean age of study participants was 40.3 years old and the median weight was approximately 73 kilograms. About a third of overall patients were from North America with just over a quarter of overall patients from the US (see Table 10).

Table 10: Baseline Demographics: Induction Phase Safety Population

Demographic Subgroup	Induction Study ITT		Non-ITT	VDZ Combined	Placebo
	Placebo	VDZ 300 mg Cohort 1[a]	VDZ 300 mg Cohort 2[b]		
N	149	225	521	746	895
Sex (n %)					
Male	92 (62)	132 (59)	301 (58)	433 (58)	525 (59)
Female	57 (38)	93 (41)	220 (42)	313 (42)	370 (41)
Age (years)					
Mean (std Dev)	41.2 (12.50)	40.1 (13.11)	40.1 (13.27)	40.1 (13.21)	40.3 (13.09)
Min, max	19, 76	18, 73	18, 78	18, 78	18, 78
Race					
White	115 (77)	183 (81)	436 (84)	619 (83)	734 (82)
Black	2 (1)	5 (2)	5 (<1)	10 (1)	12 (1)
Asian	32 (21)	36 (16)	67 (13)	103 (14)	135 (15)
Other	0	1 (< 1)	13 (2)	14 (2)	14 (2)
Weight					
(Mean ± SD), kg	72.4 (17.65)	72.4 (17.11)	74.2 (19.32)	73.6 (18.68)	73.4 (18.51)
Geographic region n (%)					
North America	63 (42)	78 (35)	189 (36)	267 (36)	330 (37)
* United States	47 (32)	64 (28)			
Western/ Northern Europe	22 (15)	40 (18)	112 (21)	152 (20)	174 (19)
Central Europe	11 (7)	25 (11)	83 (16)	108 (14)	119 (13)
Eastern Europe	13 (9)	26 (12)	37 (7)	63 (8)	76 (8)
Asia/ Australia/ Africa	40 (27)	56 (25)	100 (19)	156 (21)	196 (22)

Source: Clinical Study Report C13006, pages 111-112 and 183-184
* The US patients are a subset of the North America region
[a] Cohort 1: patients enrolled in Cohort 1 were randomized to blinded induction treatment with vedolizumab or placebo
[b] Cohort 2: patients enrolled in Cohort 2 received open-label vedolizumab induction treatment

The baseline UC disease characteristics, including duration of disease, concomitant corticosteroid and/or immunomodulator use at baseline, and prior TNFα failure were also similar across treatment arms. A comparison by treatment arms of select UC disease characteristics for the Induction Study is presented in Table 11 below.

Table 11: Comparison by Treatment Arm of Selected Baseline UC Disease Characteristics – Induction Study ITT Population

Disease Characteristic	Placebo N = 149	VDZ N = 225	P value[a]
Duration of UC (years) [b] Mean (std dev)	7.1 (7.25)	6.1 (5.08)	0.8432
Baseline disease activity [c] Mean (std dev)	8.6 (1.68)	8.5 (1.78)	0.7276
Corticosteroid use at baseline or randomization, n (%)			
Yes	84 (56)	126 (56)	0.9428
No	65 (44)	99 (44)	
Immunomodulator use at baseline or randomization. n (%)			
Yes	44 (30)	75 (33)	0.4395
No	105 (70)	150 (67)	
Prior TNFα use, n (%)			
Yes	73 (49)	95 (42)	0.1975
No	76 (51)	150 (58)	
Prior TNFα failure, n (%)			
Yes	63 (42)	82 (36)	0.2567
No	86 (58)	143 (64)	

Source: Clinical Study Report C13006, Table 14, page 119
[a] p values for categorical variables are from chi-square test and for continuous variables are from Kruskal Wallis test.
[b] Duration of ulcerative colitis is defined as (1 + first dose date – diagnosis date)/365.25
[c] Baseline disease activity represents the baseline complete Mayo score.

Reviewer comment: the demographics are well balanced between treatment arms. Approximately ¼ of patients in the ITT populations were from the United States in both the Induction and Maintenance Studies. This is relevant, as the US population had stricter enrollment criteria and did not allow concomitant immunosuppressants, beyond Week 6 of the Induction Phase. There is a higher proportion in patients from North America in the VDZ Q8W group, however, the results were consistent when comparing both the Q8W and Q4W groups with placebo, so this did not appear to impact the results. This is discussed further in Sections 6.1.3 and 6.1.4 below.

Maintenance Phase

The baseline demographics were also similar among treatment arms in the Maintenance Phase with the exception of geographic distribution. Patients from North America appeared to be more likely to be in the VDZ Q8W treatment arm (40%) compared to the VDZ Q4W (30%) or placebo (29%). There was also a higher proportion of patients from Asia/Australia/Africa randomized to the placebo arm, as compared to the VDZ Q8W or VDZ Q4W (27%, 15%, and 22%, respectively). The distribution was similar across treatment groups in other geographic regions. Baseline demographic characteristics for the Maintenance Phase safety population are presented in Table 12 below.

Table 12: Baseline Demographics: Maintenance Phase Safety Population

Demographic Subgroup	Maintenance Study ITT			Non-ITT		VDZ Combined
	Placebo	VDZ 300mg Q8W	VDZ 300 mg Q4W	Placebo	VDZ Q4W	
N	126	122	125	149	373	620
Sex (n %)						
Male	69 (55)	70 (57)	68 (54)	92 (62)	226 (61)	364 (59)
Female	57 (45)	52 (43)	57 (46)	57 (38)	147 (39)	256 (41)
Age (years)						
Mean (std Dev)	40.3 (13.92)	41.0 (12.85)	38.6 (14.21)	41.2 (12.50)	40.3 (12.73)	40.1 (13.07)
Min, max	18, 74	19, 78	19, 76	19, 76	19, 75	19, 78
Race						
White	101 (80)	104 (85)	101 (81)	115 (77)	313 (84)	518 (84)
Black	2 (2)	4 (3)	1 (<1)	2 (1)	3 (<1)	8 (1)
Asian	20 (16)	13 (11)	21 (17)	32 (21)	49 (13)	83 (13)
Other	3 (2)	1 (<1)	2 (2)	0	8 (2)	11 (2)
Weight						
(Mean ± SD), kg	74.7 (20.42)	78.2 (18.76)	71.8 (16.71)	72.4 (17.65)	72.4 (18.48)	73.4 (18.32)
Geographic region n (%)						
North America	36 (29)	49 (40)	37 (30)	62 (42)	145 (39)	231 (37)
* United States	24 (19)	36 (30)	24 (19)			
Western/ Northern Europe	20 (16)	23 (19)	25 (20)	22 (15)	84 (23)	42 (15)
Central Europe	26 (21)	20 (16)	25 (20)	11 (7)	37 (10)	82 (13)
Eastern Europe	10 (8)	12 (10)	11 (9)	13 (9)	30 (8)	53 (9)
Asia/ Australia/ Africa	34 (27)	18 (15)	27 (22)	40 (27)	77 (21)	122 (20)

Source: Clinical Study Report C13006, Table 44, pages 183-184
* The US patients are a subset of the North America region

As in the Induction Phase, the baseline UC disease characteristics were also similar across treatment arms. A comparison by treatment arms of select UC disease characteristics for the Maintenance Study is presented in Table 13 below.

Table 13: Comparison by Treatment Arm of Selected Baseline UC Disease Characteristics – Maintenance Study ITT Population

Disease Characteristics	Placebo N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	P value [a]
Duration of UC (years) [b] Mean (std dev)	7.8 (6.88)	6.2 (4.76)	7.6 (7.02)	0.5242
Baseline disease activity [c] Mean (std dev)	8.4 (1.75)	8.4 (1.80)	8.3 (1.66)	0.7635
Corticosteroid use at baseline or randomization, n (%)				
Yes	72 (57)	70 (57)	73 (58)	0.9774
No	54 (43)	52 (43)	52 (42)	
Immunomodulator use at baseline or randomization. n (%)				
Yes	51 (40)	43 (35)	45 (36)	0.6524
No	75 (60)	79 (65)	80 (64)	
Prior TNFα use, n (%)				
Yes	47 (37)	50 (41)	52 (42)	0.7540
No	79 (63)	72 (59)	73 (58)	
Prior TNFα failure, n (%)				
Yes	38 (30)	43 (35)	40 (32)	0.6878
No	88 (70)	79 (65)	85 (68)	

Source: Clinical Study Report C13006, Table 49, page 194
[a] p values for categorical variables are from chi-square test and for continuous variables are from Kruskal Wallis test.
[b] Duration of ulcerative colitis is defined as (1 + first dose date – diagnosis date)/365.25
[c] Baseline disease activity represents the baseline complete Mayo score.

Reviewer comment: The baseline demographics and disease characteristics were generally similar across treatment arms. There is a higher proportion in patients from North America in the VDZ Q8W group; however, the results were consistent when comparing both the Q8W and Q4W groups with placebo, so this did not appear to impact the results. This is discussed further in Sections 6.1.3 and 6.1.4 below.

6.1.3 Subject Disposition

Patients who discontinued from Study C13006 for any reason were to return to clinic at the earliest opportunity to complete the Early Termination visit. The possible reasons for discontinuation from the study drug were: adverse events (AE), withdrawal by patient, study terminated by the sponsor, protocol violation(s), lost-to-follow up, lack of efficacy, and other (specify). Patients who withdrew from the study were not replaced.

Patients who withdrew early were eligible for rollover into Study C13008 if they withdrew for one of the following reasons:

- sustained nonresponse: failure to achieve clinical response by Week 14
- disease worsening: an increase in partial Mayo score of ≥ 3 points on 2 consecutive visits from the Week 6 value and a minimum partial Mayo score of ≥ 5 points
- required rescue medications at Week 14 or beyond

C13006 Induction Phase

There were 374 patients included in Cohort 1 who were randomized to placebo (149) or vedolizumab 300 mg (225). The randomization was stratified for two factors that are markers of disease severity: concomitant use of oral corticosteroids: and previous exposure to TNFα antagonists or concomitant immunomodulator (6-mercaptopurine or azathioprine) use. The Applicant included all randomized patients who received at least one dose of study drug in the ITT population of the Induction Study. The PP population was a subset of the ITT population which excluded patients who did not meet specific entry criteria or had certain protocol violations.

Twenty-one (21) patients discontinued from the Induction Study prior to completion, and the primary reasons for discontinuation were AEs and lack of efficacy. An additional 36 patients from Cohort 2 discontinued prior to completion of the Induction Phase. A greater percentage of patients in the placebo arm discontinued early overall, as well as specifically for AEs and lack of efficacy. Of note, many of the AEs leading to discontinuation were related to the underlying disease and likely also represent lack of efficacy.

Table 14: Patient Disposition, C13006 Induction Phase

	Induction Study Cohort 1		Non-ITT Cohort 2	Combined	
	PLA N = 149	VDZ N = 225	VDZ N = 521	VDZ Combined N = 746	Total N = 895
Randomized	149	225	521	746	895
Safety Population[a]	149 (100)	225 (100)	521 (100)	746 (100)	895 (100)
ITT Population[b]	149 (100)	225 (100)	-	225 (30)	374 (42)
PP Population[c]	138 (93)	215 (96)	-	215 (29)	353 (39)
Completed Study[d]	135 (91)	218 (97)	485 (93)	703 (94)	838 (94)
Discontinued (Reason)	14 (9)	7 (3)	36 (7)	43 (6)	57 (6)
Adverse Event	4 (3)	0	7 (1)	7 (<1)	11 (1)
Protocol Violation(s)	1 (<1)	1 (<1)	6 (1)	7 (<1)	8 (<1)
Lack of Efficacy	5 (3)	2 (<1)	14 (3)	16 (2)	21 (2)
Withdrawal of Consent	3 (2)	4 (2)	8 (2)	12 (2)	15 (2)
Lost to Follow-Up	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)

Source: Clinical Study Report C13006 Table 6, page 108
Note: no patients discontinued from Study C13006 for a reason of: Study Terminated by Sponsor or Other
[a] Safety Population: All patients in Cohort 1 and 2 who received any amount of study drug in the Induction Phase, according to the actual study drug received.
[b] ITT: All randomized patients in Cohort 1 who received any amount of blinded study drug.
[c] PP: All Induction Study ITT patients without any major protocol deviations.
[d] Completed Study: Patients who completed dosing at Weeks 0 and 2 and completed the predose assessments at Week 6.

Reviewer comment: The number of early discontinuations from the Induction Study was small and should not impact results. Only 1 patient (placebo arm) in the Induction Study was lost to follow up. A numerically higher proportion of patients from the non-ITT (Cohort 2) VDZ group discontinued due to lack of efficacy, as compared to the Cohort 1 VDZ group, however, these numbers were still fairly low. This is unlikely to have an impact on the trial outcome.

Twenty-four patients from the ITT population did not meet entry criteria in the Induction Study and 20 of these patients were also included in the PP analysis population. Table 15 below summarizes these patients.

Table 15: Summary of Induction Study PP Patients who did not Meet I/E Criteria

Type of Unmet Criteria Patients with at Least One Unmet Entry Criterion	PLA N = 149	VDZ N = 225	Total N = 373
Pts with at Least 1 Unmet Entry Criterion	13	11	24
Inclusion Criteria			
Inadequate or lost response/intolerance of steroids, immunomodulators, and/or anti-TNFs	3 (2)[a]	5 (2)	8 (2)
Initial steroid dose stable x 4 weeks or 2 weeks for tapering steroids	2 (1)	2 (<1)	4 (1)
UC diagnosed ≥ 6 months prior to enrollment	2 (1)	0	2 (<1)
Gastrointestinal Exclusion Criteria			
C. difficile infection within 60 days or other intestinal pathogen within 30 days prior to enrollment	5 (3)[b]	0	5 (1)
Use of non-biologic therapies (e.g. cyclosporine) for the treatment of UC within 30 days prior to enrollment	0	1 (<1)	1 (<1)
Colonic mucosal dysplasia	0	1 (<1)	1 (<1)
5-ASA or steroid enemas/suppositories within 2 weeks of first dose	0	1 (<1)	1 (<1)
Infectious Disease Exclusion Criteria			
A positive TB test within 1 month	2 (1)[c]	1 (<1)[c]	3 (<1)
TB on CXR within 3 months	1 (<1)	0	1 (<1)

Source: Clinical Study Report C13006, pages 107 - 109

[a] 1 patient from the placebo arm who did not demonstrate an inadequate response/intolerance of steroids, immunomodulators, and/or anti-TNFs, was excluded from the PP population

[b] 1 patient from the placebo arm who had evidence of a C diff infection was excluded

[c] 1 patient each from the PLA and VDZ arms who had a positive TB test within 1 month were excluded from the PP population

Reviewer Comment: The number of patients not meeting entry criteria but included in the ITT and/or PP populations was evenly divided between the placebo and vedolizumab arm and should not affect the results. In addition, the applicant performed a number of sensitivity analyses for the primary and secondary efficacy endpoints, which show consistency of results. These results are provided in Section 6.1.4 below.

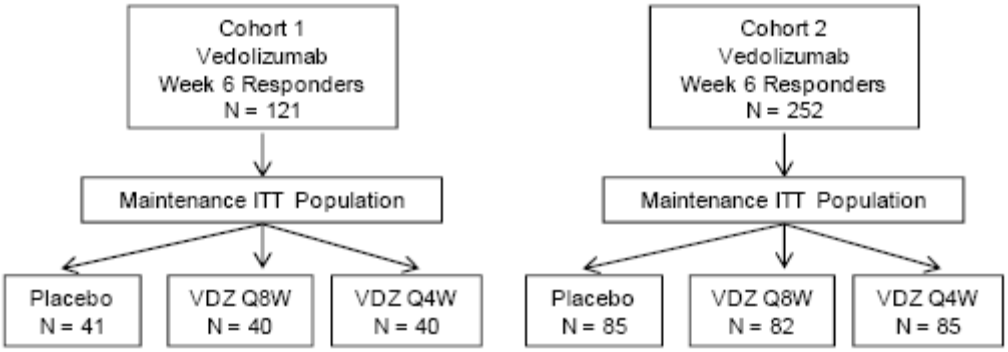
C13006 Maintenance Study

There were 373 patients randomized in the Maintenance Study. One hundred and twenty-one (121) of these patients (54%) were from Cohort 1 and 252 (48%) were from Cohort 2 of the Induction Phase. These patients were randomized to placebo (126), vedolizumab 300 mg Q4W (122), and vedolizumab 300 mg Q8W (125). Randomization was stratified by three factors: enrollment in Cohort 1 or Cohort 2 in the Induction Phase; concomitant use of oral corticosteroids; and previous exposure to TNFα antagonists or concomitant immunomodulator use. An additional 373 vedolizumab-treated patients who did not demonstrate response at Week 6 of the Induction Phase were considered part of the non-ITT vedolizumab group and continued with

vedolizumab infusions every 4 weeks through Week 52. One hundred forty-nine (149) patients who received double-blind placebo during the Induction Phase continued on placebo infusions every 4 weeks during the Maintenance Phase as part of the non-ITT placebo group, and were included in the safety assessments.

For the maintenance efficacy analyses, the ITT population was defined as all randomized patients who received vedolizumab during the Induction Phase and met the protocol definition of clinical response at Week 6, as assessed by the investigator, were randomized, and received any amount of double-blind study drug in the Maintenance Phase. Patients from Cohort 1 and Cohort 2 were evenly distributed between treatment arms, as shown in Figure 4 below.

Figure 4: Summary of Patient Disposition in Maintenance Study, by Cohort



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There were 164 patients (44%) who discontinued from the Maintenance Study prior to completion, and the majority of these patients were from the placebo arm (78 patients, 62%). The primary reason for discontinuation was lack of efficacy, and more patients discontinued due to lack of efficacy from the placebo arm (61 patients, 48%) than from either vedolizumab arm (31 patients, 25% and 33 patients, 26% from the Q8W and Q4W, respectively). A greater number of patients in the placebo arm discontinued early for AEs as well; however, many of these AEs were disease related and likely represent lack of efficacy and not a true AE. See Table 16 below, for additional details.

Table 16: Patient Disposition – Maintenance Phase

	Maintenance Study			Non-ITT		Combined	
	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA[b] N = 149	VDZ Q4W[c] N = 373	PLA N = 275	VDZ N = 620
Completed Induction Treatment	126 (100)	122 (100)	125 (100)	135 (91)	330 (88)	261 (95)	577 (93)
Randomized	126 (100)	122 (100)	125 (100)	149 (100)	373 (100)	275 (100)	620 (100)
Safety Population[d]	126 (100)	122 (100)	125 (100)	149 (100)	373 (100)	275 (100)	620 (100)
ITT Population[a]	126 (100)	122 (100)	125 (100)	-	-	126 (46)	247 (40)
PP Population[e]	121 (96)	117 (96)	121 (97)	-	-	121 (44)	238 (38)
Completed Maintenance Phase[f]	48 (38)	77 (63)	84 (67)	30 (20)	135 (36)	78 (28)	296 (48)
Discontinued (Reason)[g]	78 (62)	45 (37)	41 (33)	119 (80)	238 (64)	197 (72)	324 (52)
Adverse Event	15 (12)	7 (6)	6 (5)	16 (11)	23 (6)	31 (11)	36 (6)
Protocol Violation(s)	0	0	0	2 (1)	9 (2)	2 (<1)	9 (1)
Lack of Efficacy	61 (48)	31 (25)	33 (26)	88 (59)	171 (46)	149 (54)	235 (38)
Withdrawal of Consent	2 (2)	5 (4)	2 (2)	9 (6)	32 (9)	11 (4)	39 (6)
Lost to Follow-Up	0	2 (2)	0	4 (3)	3 (<1)	4 (1)	5 (<1)

Source: Clinical Study Report C13006 Table 41, page 176-177
Note: no patients discontinued from Study C13006 for a reason of: Study Terminated by Sponsor or Other
[a] The Maintenance Study ITT consisted of all randomized patients who received any amount of blinded study drug
[b] Patients who received placebo during the Induction Phase and continued to receive placebo during the Maintenance Phase
[c] Patients who received vedolizumab in the Induction Phase but did not achieve clinical response at Week 6 and continued to receive vedolizumab every 4 weeks during the Maintenance Phase
[d] The safety population consists of all patients who received any amount of study drug at any time in the study, based on what they actually received.
[e] Maintenance Study PP population consists of all Maintenance Study ITT patients without any major protocol deviations
[f] Completed study is defined as patients who completed the Week 52 analyses
[g] Includes patients who discontinued at any time during the study, even before Week 6

Reviewer comment: There were a large number of discontinuations in the Maintenance Phase with a higher number of discontinuations from the placebo arm. This is not surprising in a study of this length, where patients are continued on placebo for an extended period of time; however, disproportionate discontinuations have the potential to impact Maintenance Study results. A number of sensitivity analyses were performed post hoc by the sponsor and additional analyses performed after request from the Division in an information request. These results are provided in Section 6.1.4 and show internal consistency. This supports that the Maintenance Study results were not impacted by patient discontinuations.

Only two patients (Q8W vedolizumab arm) in the Maintenance Study were lost to follow up. This is unlikely to have an impact on the trial outcome. Approximately 2% of

patients withdrew consent, and no additional information is provided. This is a small percent of the overall population, however, and those who withdrew consent are evenly distributed across treatment arms. This should not impact results.

Eighteen patients from the Maintenance ITT population did not meet entry criteria for the Maintenance Study. Fourteen of these patients were also included in the PP analysis population. This is summarized in Table 17, below.

Table 17: Summary of Maintenance Study PP Patients who did not Meet I/E Criteria

Type of Unmet Criteria	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	Total N = 373
Pts with at Least 1 Unmet Entry Criterion	7	6	5	18
Inclusion Criteria				
Inadequate or lost response/intolerance of steroids, immunomodulators, and/or anti-TNFs	2 (2)	2 (2)	1 (<1)	5 (1)
Criteria for stability of corticosteroid dosing prior to enrollment	0	0	1 (<1)	1 (<1)
Stable dose of azathioprine or 6-mercaptopurine for 8 weeks prior to enrollment	1 (<1)	0	0	1 (<1)
Colonoscopy within 12 months prior to screening for patients with long-standing disease	0	0	1 (<1)	1 (<1)
Mayo score of 6 to 12 with an endoscopic subscore ≥ 2	2 (2)[a]	0	1 (<1)[a]	3 (1)
Gastrointestinal Exclusion Criteria				
C. difficile infection within 60 days or other intestinal pathogen within 30 days prior to enrollment	0	2 (2)	1 (<1)	3 (1)
Use of non-biologic therapies (e.g. cyclosporine) for the treatment of UC within 30 days prior to enrollment	2 (2)[b]	0	0	2 (<1)
5-ASA or steroid enemas/suppositories within 2 weeks of first dose	0	1 (<1)	0	1 (<1)
General Exclusion Criteria				
Positive PML subjective symptom checklist	0	1 (<1)	0	1 (<1)

Source: Clinical Study Report C13006, pages 176 - 180
[a] 3 patients who did not meet Mayo score criteria (2 from placebo and 1 from VDZ Q4W arm) were excluded from the PP population
[b] 1 patient from the placebo arm who used non-biologic therapies within 30 days of enrollment was excluded from the PP population

In addition to the patients summarized in Table 17 above, 41 patients were assessed as having clinical response by the investigator but did not meet the protocol definition for clinical response. This is summarized in Table 18. These patients should not have been included in the Maintenance Study. A sensitivity analysis was completed by the applicant, to assess the impact of the inclusion of these patients on the proportion of patients in clinical remission at Week 52, and results are provided in Section 6.1.4.

Table 18: Patients in Maintenance ITT who did not Achieve Clinical Response at Week 6

Type of Unmet Criteria	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	Total N = 373
Did not meet protocol definition of complete response	16	11	14	41

Source: Clinical Study Report C13006, pages 197 - 198

Reviewer comment: As in the Induction Study, multiple patients included in the ITT and PP populations did not meet entry criteria. In particular, 18 patients in the Maintenance Study did not meet prespecified entry criteria. These patients appear to be evenly distributed between treatment arms; however, so this should not impact the efficacy results. As in the Induction Study, a number of sensitivity analyses for the primary and secondary efficacy endpoints were performed and showed consistency of the reported results. A sensitivity analysis excluding patients who did not achieve clinical response at Week 6 continued to show both vedolizumab dosing regimens were significantly better than placebo ($p < 0.0001$). These results are provided in Sections 6.1.4 and 6.1.5, below.

6.1.4 Analysis of Primary Endpoint(s)

Induction Study:

Primary Analysis

The primary endpoint for the Induction Study was the proportion of patients with clinical response at Week 6, where clinical response was defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

The primary analysis population for the primary endpoint analysis was the ITT population, as specified in Table 9 above. Patients with missing data were considered non-responders. The primary comparison was tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to

- concomitant use of oral corticosteroids
- previous exposure to TNFα antagonists or concomitant immunomodulator use.

The proportion of patients in clinical response at Week 6 was significantly greater in the vedolizumab group (47.1%) relative to placebo (25.5%). The difference from placebo was 21.7% (95% CI: 11.6, 31.7; p< 0.0001).

Table 19: Clinical Response at Week 6 – ITT population

Clinical Response	Placebo N = 149	Vedolizumab 300 mg N = 225
Number (%) achieving clinical response	38 (25.5)	106 (47.1)
95% CI	(18.5, 32.5)	(40.6, 53.6)
Difference from placebo		21.7
95% CI for difference from placebo		(11.6, 31.7)
P value for difference from placebo		< 0.0001

Source: Clinical Study Report C13006, Table 18, page 121

Sensitivity Analyses

Several prespecified sensitivity analyses were performed with the PP and Completer populations. In addition, post hoc analyses were completed using different missing data imputation methods including a worst case analysis and Last Observation Carried Forward (LOCF) analysis. The results of each of these sensitivity analysis, including the Worst Case analysis, favored vedolizumab. Also, as previously described in Section 5.3.9, an exploratory analysis was performed considering all patients non-responders if less than 3 days of diary data were available within 7 days prior to Week 6. The results from this analysis were unchanged from the primary analysis. The results of the sensitivity analyses are shown in Table 20 below

Table 20: Clinical Response at Week 6 – Sensitivity Analyses

Analysis Set	Placebo	Vedolizumab 300 mg	Difference (vedolizumab – placebo)	p-value
Per Protocol	38/138 (27.5%)	106/215 (49.3%)	21.8%	< 0.0001
Completers (Observed Case)	38/137 (27.7%)	106/216 (49.1%)	21.5%	< 0.0001
ITT with Revised eDiary Requirements[a]	38/149 (25.5%)	106/225 (47.1%)	21.7%	< 0.0001
LOCF[b]	39/149 (26.2%)	106/225 (47.1%)	21.0%	< 0.0001
Worst Case[c]	50/149 (33.6%)	106/225 (47.1%)	13.6%	0.0088

Source: Clinical Study Report C13006 Tables 14.3.1.2C and 14.3.1.2B and 1.11.3 Responses to Agency Questions

[a] ITT population where patients with < 3 days of diary data within 7 days prior to Week 6 are classified as non-responders

[b] Last Observation Carried Forward (LOCF) analysis imputed data from the prior time point, if a subject had missing data at a particular time point.

[c] Worst Case analysis assumed patients receiving placebo who had missing data to be responders and patients receiving vedolizumab who had missing data to be non-responders

Reviewer comment: The results of the various sensitivity analyses are consistent and remain highly statistically significant for all but the Worst Case analysis. The Worst Case analysis is biased against the vedolizumab group because it considers placebo dropouts as responders, but the results from this analysis still favor vedolizumab. This reviewer believes the sensitivity analyses performed by the applicant support the consistency of the data and does not believe the results were impacted by missing data. Please see the Statistical Review by Milton Fan, PhD for additional information.

Subgroup Analyses

All subgroup analyses throughout this document are exploratory, as the study was not powered for these assessments. Patients with moderately to severely active UC who have failed TNFα agents are a particularly difficult to treat group and have few other medical treatment options for UC. This subgroup was thus of specific interest and the primary endpoint was analyzed as an exploratory endpoint by treatment for the subgroup of patients who previously failed TNFα. The Applicant included patients who failed, lost response to, or were intolerant of TNFα agents as TNFα failures. In this subgroup of patients, vedolizumab appeared more effective than placebo with 39% in clinical response at Week 6 versus 20% for placebo, an 18.4% treatment difference. A stricter definition for TNFα failure would include only those patients who failed to respond or lost response to TNFα agents. Table 21 provides the results using both definitions for TNFα failure.

Table 21: Clinical Response at Week 6 – Subgroup Analysis prior TNFα failures

Endpoint	Patients Without Prior Failure		Patients with Prior Failure	
	Placebo	Vedolizumab 300 mg	Placebo	Vedolizumab 300 mg
Protocol Defined TNFα Failure[a]				
N	76	130	63	82
Number (%) achieving response	20 (26.3%)	69 (53.1%)	13 (20.0%)	32 (39.0%)
95% CI	(16.4, 36.2)	(44.5, 61.7)	(10.6, 30.6)	(28.5, 49.6)
Difference from placebo (95%CI)		26.8 (13.7, 39.9)		18.4 (3.9, 32.9)
Patients who failed to respond to or lost response to TNFα agents				
N	94	149	55	76
Number (%) achieving response	26 (27.7%)	77 (51.7%)	12 (21.8%)	29 (38.2%)
95% CI	(18.6, 36.7)	(43.7, 59.7)	(10.9, 32.7)	(27.2, 49.1)
Difference from placebo		24		16.4

Source: Clinical Study Report C13006 Table 21 pg. 133 and 1.11.3 Responses to Agency Questions
[a] Protocol defined TNFα failure includes those patients who failed to respond to, lost response to, or were intolerant of TNFα agents

In Study C13006, the US population varied from the ex-US population, both in entry criteria and in its allowance of concomitant immunosuppressant use. In the US, patients were required to have failed either an immunomodulator (5-mercaptopurine or azathioprine) or a TNFα agent, while outside the US failing corticosteroids was sufficient for study entry. In addition, outside the US, patients could continue concomitant immunomodulator therapy over the course of the trial, while in in the US only patients in Cohort 1 could be receiving concomitant immunomodulators at the start of the trial, and these patients were required to discontinue immunomodulators at Week 6. A post hoc subgroup analysis for all patients meeting the US criteria was completed, whether or not they were enrolled in the US. Overall, 49% of the patients enrolled in C13006 met the US protocol criteria. These results are provided below:

Table 22: Clinical Response at Week 6 – Subgroup Analysis Based on the US Protocol Criteria Status

Clinical Response[a]	Placebo N = 149	Vedolizumab N = 225
US Protocol Criteria Met[b]	85	112
Number (%) achieving response	20 (23.5)	42 (37.5)
95% CI	(14.5, 32.5)	(28.5, 46.5)
Difference from placebo (95% CI)		14.0 (1.3, 26.7)
US Protocol Criteria Not Met	64	113
Number (%) achieving response	18 (28.1)	64 (56.6)
95% CI	(17.1, 39.1)	(47.5, 65.8)
Difference from placebo (95% CI)		28.5 (14.2, 42.8)

Source: Table 38.3.1.1A of response to questions clinical august 8 2013, page 25

[a] Clinical response is defined as reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point
Confidence intervals for categorical data with numerators less than or equal to five are from the exact method, otherwise from normal approximation

[b] US protocol criteria required patients to have failed either an immunomodulator (5-mercaptopurine or azathioprine) or a TNFα agent, while outside the US failing corticosteroids was sufficient for study entry. In addition, US criteria status required patients to discontinue immunomodulators by Week 6.

Finally, subgroup analyses based on age and gender showed a numerically higher response rate with vedolizumab. Other subgroup analyses with smaller sample sizes (race, region, disease localization, Mayo score category) also favored vedolizumab. These results are summarized in section 6.1.7

Reviewer comments: Vedolizumab appeared to be slightly less effective in the subgroup of patients who previously failed TNFα agents, however, even in the more difficult to treat patients (i.e., patients who previously failed TNFα), the results favor vedolizumab. Similarly, vedolizumab had numerically higher response rates in the group of patients who did not meet the stricter US protocol criteria, but the results favor vedolizumab in both subgroups. The results were consistent across a variety of subgroups, including age, gender, race, duration of disease, geographic region, and baseline disease activity, as well as anti-TNF users and failures. While the study was not powered for key subgroup analyses and there was no multiplicity adjustment, because the subgroup analyses were consistent with the overall results this reviewer feels they can generally be believed.

Maintenance Study:

Primary Analysis:

The primary endpoint for the Maintenance Study was the proportion of patients in clinical remission at 52 weeks, where clinical remission was defined as total Mayo score of ≤ 2 points with no individual subscore > 1 point.

For both assessments of the primary endpoint, the CMH chi-square test was used to compare the two treatment groups at the 5% level of significance with stratification according to enrollment in Cohort 1 or 2 in the Induction Phase, concomitant use of oral corticosteroids, and previous exposure to TNFα antagonists or concomitant immunomodulator use. In comparison to placebo, each of the two vedolizumab dosing regimens showed significant improvement on the pre-specified definition of remission. In the Q8W dosing group, the difference from placebo was 26.1%, and in the Q4W group, the difference was 29.1%, with $p < 0.0001$ for both groups.

Table 23: Clinical Remission at Week 52 – ITT Population

Clinical Remission	Placebo	Vedolizumab 300 mg Q8W	Vedolizumab 300 mg Q4W
N	126	122	125
Number (%) achieving response	20 (15.9%)	51 (41.8%)	56 (44.8%)
95% CI	(9.5, 22.3)	(33.1, 50.6)	(36.1, 53.5)
Difference from placebo		26.1	29.1
95% CI for difference from placebo		(14.9, 37.2)	(17.9, 40.4)
P value for difference from placebo		< 0.0001	< 0.0001

Source: Clinical Study Report C13006, Table 52 page 197

Reviewer comment: The results for the primary efficacy analysis for maintenance, maintenance of remission, are highly statistically significant in both vedolizumab treatment arms, compared to placebo. It should be noted, however, that the applicant included all patients in clinical response at Week 6 in the analysis population and did not stratify by remission status. The proportion of patients in clinical remission at Week 6 by Induction Cohorts was similar across treatment arms. In addition, the prespecified secondary endpoint of durable clinical remission (defined as the proportion of patients in clinical remission at Weeks 6 and 52) was analyzed, and the results are consistent with the primary endpoint. This reviewer believes these results can be believed and can support a claim of maintenance of clinical remission.

Sensitivity Analyses:

As previously noted, the prespecified definition for clinical remission was a complete Mayo score of ≤ 2 points and no individual subscore > 1 point, and this definition was agreed upon by the Division. A more stringent definition of clinical remission requires both the rectal bleeding and endoscopy subscores must equal 0, underscoring the importance of lack of friability and absence of rectal bleeding in assessing a patient's remission status. A post hoc sensitivity analysis was completed using the more stringent definition. The results were nominally significant, and a table comparing the results using both definitions for clinical remission is shown in Table 24 below.

Table 24: Clinical Remission Week 52: Prespecified and FDA defined.

Analysis Set	Placebo	VDZ 300 mg Q8W	Difference (VDZ – placebo)	p-value	VDZ 300 mg Q4W	Difference (VDZ – placebo)	p-value
ITT	20/126 (15.9%)	51/122 (41.8%)	26.1%	< 0.0001	56/125 (44.8%)	29.1%	< 0.0001
ITT – FDA definition	11/126 (8.7%)	32/122 (26.2%)	17.6%	0.0002	36/125 (28.8%)	20.2%	< 0.0001

Source: Clinical Study Report C13006 and Report on Supplemental Efficacy Analyses Requested by the FDA for Study C13006

The results of prespecified sensitivity analyses using the PP and Completers (Observed Case) populations also showed significant treatment differences favoring vedolizumab. As previously noted in Section 6.1.3 above, 41 patients were included in the Maintenance Study ITT and PP population who did not meet the protocol definition for clinical response. A post hoc sensitivity analysis was completed to assess the impact of the inclusion of these patients in the Maintenance Study.

An exploratory analysis was also performed considering patients non-responders if they had less than three days of diary data available within seven days prior to a study visit. The results were consistent with both vedolizumab dosing regimens remaining significantly better than placebo. In the Q8W dosing group, the difference from placebo was 23.6%, and in the Q4W group, the difference was unchanged from the primary analysis (29.1%), with $p < 0.0001$ for both groups. Finally post hoc analyses were completed using different missing data imputation methods. The results are shown in Table 25 below.

Table 25: Clinical Remission at Week 52 - Sensitivity Analyses

Analysis Set	Placebo	Vedolizumab 300 mg Q8W	Difference (vedolizumab – placebo)	p-value	Vedolizumab 300 mg Q4W	Difference (vedolizumab – placebo)	p-value
PP	20/121 (16.5%)	49/117 (41.9%)	25.7%	< 0.0001	55/121 (45.5%)	29.1%	< 0.0001
Completers (Observed Case)	20/48 (41.7%)	51/77 (66.2%)	24.1%	0.0079	56/83 (67.5%)	25.0%	0.0042
ITT - Met Criteria for Complete Response	20/110 (18.2%)	50/111 (45.0%)	27.6%	< 0.0001	52/111 (46.8%)	28.2%	< 0.0001
ITT with Revised eDiary Requirements[b]	11/126 (8.7%)	22/122 (18.0%)	9.3%	0.0294	30/125 (24.0%)	15.3%	0.0009
LOCF[c]	27/126 (21.4%)	57/122 (46.7%)	25.4%	< 0.0001	58/125 (46.4%)	25.2%	< 0.0001
Worst Case[d]	98/126 (77.8%)	51/122 (41.8%)	- 36.0%	<0.0001	56/125 (44.8%)	- 32.9%	< 0.0001

Source: Clinical Study Report C13006 Tables 14.3.1.2CM and 14.3.1.2BM and 1.11.3 Responses to Agency Question
[a] This analysis does not include the 41 patients who did not meet the protocol definition for complete response but were included in the Maintenance Study ITT and PP population
[b] ITT population where patients with < 3 days of diary data within 7 days prior to Week 52 are classified as non-responders
[c] Last Observation Carried Forward (LOCF) analysis imputed data from the prior time point, if a subject had missing data at a particular time point.
[d] Worst Case analysis assumed patients receiving placebo who had missing data to be responders and patients receiving vedolizumab who had missing data to be non-responders

Reviewer Comment: The Division currently believes the absence of rectal bleeding and lack of friability on endoscopy are important components for clinical remission. The results of the primary efficacy analysis are statistically significant, whether the prespecified or more stringent definition for clinical remission is used. In addition, the results of the various sensitivity analyses are statistically significant and generally consistent with the primary analysis. The Worst Case analysis favors placebo, however, this analysis is particularly biased during the Maintenance Phase, as there was a high rate of placebo drop out due to lack of efficacy and UC flares. Considering these patients as responders is biased against the vedolizumab group and should be considered with caution. This reviewer believes the sensitivity analyses performed by the applicant support the efficacy of vedolizumab in maintaining remission and believes the impact of missing data was adequately assessed by the Applicant. Please see Dr Milton Fan's statistical review for additional information.

Subgroup Analyses:

As described in the Induction Study results section, a prespecified subgroup analysis was performed in patients who have failed to respond to, lost response to, or became intolerant of TNFα agents. This definition of prior TNF failure was agreed upon; however, a post hoc analysis was performed in only those patients who failed to respond to or lost response to TNFα agents. With both definitions, the results remained

consistent with the primary efficacy analysis, and favored vedolizumab over placebo. Table 26 provides the results for both of these subgroups.

Table 26: Clinical Remission at Week 52 – Subgroup Analysis prior TNFα failures

Endpoint	Patients Without Prior Failure[a]			Patients with Prior Failure[a]		
	Placebo	VDZ 300 mg Q8W	VDZ 300 mg Q4W	Placebo	VDZ 300 mg Q8W	VDZ 300 mg Q4W
Protocol Defined TNFα Failure[a]						
N	79	72	73	38	43	40
Number (%) achieving remission	15 (19.0)	33 (45.8)	35 (47.9)	2 (5.3)	16 (37.2)	14 (35.0)
95% CI	(10.3, 27.6)	(34.3, 57.3)	(36.5, 59.4)	(0.6, 17.7)	(23.0, 53.3)	(20.6, 51.7)
Difference from placebo (95%CI)		26.8	29.0		31.9	29.7
Patients who failed to respond to or lost response to TNFα agents						
N	94	90	93	32	32	32
Number (%) achieving remission	18 (19.1)	41 (45.6)	48 (51.6)	2 (6.3)	10 (31.3)	8 (25.0)
95% CI	(11.2, 27.1)	(35.3, 55.8)	(41.5, 61.8)	(0.8, 20.8)	(16.1, 50.0)	(11.5, 43.4)
Difference from placebo (95%CI)		26.4	32.5		25.0	18.8

Source: Clinical Study Report C13006 and Response to Agency Questions Received September 20, 2013 (1.11.3)
[a] Protocol defined TNFα failure includes those patients who failed to respond to, lost response to, or were intolerant of TNFα agents
[b] Failure as defined by each of the subgroup analyses: 1. failed to respond to, lost response to, or become intolerant of TNFα agents or 2. failed to respond to or lost response to TNFα agents

The Maintenance Study included patients who achieved clinical response to vedolizumab induction treatment, whether they were included in Cohort 1 or Cohort 2 of the Induction Phase. Patients in Cohort 1 received blinded treatment and were part of the Induction Study efficacy analyses, however, patients in Cohort 2 received open-label vedolizumab and enrolled in the Induction Phase to ensure that the sample size of induction responders was sufficient to power the Maintenance Study. A subgroup analysis on the number and proportion of patients in the Maintenance Study ITT population who achieved clinical remission at Week 52 by Induction Phase Cohort was performed.

Table 27: Clinical Remission at Week 52 by Induction Phase Cohort

Clinical Remission, n (%)	Cohort 1[a]			Cohort 2[b]		
	Placebo N = 41	VDZ 300 mg Q8W N = 40	VDZ 300 mg Q4W N = 40	Placebo N = 85	VDZ 300 mg Q8W N = 82	VDZ 300 mg Q4W N = 85
Number achieving clinical remission	6 (14.6)	19 (47.5)	20 (50.0)	14 (16.5)	32 (39.0)	36 (42.4)
95% CI	(3.8, 25.5)	(32.0, 63.0)	(34.5, 65.5)	(8.6, 24.4)	(28.5, 49.6)	(31.8, 52.9)
Difference from placebo (95%CI)		33.2	36.3		22.6	25.7
p-value for difference from placebo		0.0012	0.0004		0.0009	0.0002

Source: Report on Supplemental Efficacy Analyses Requested by the FDA for Study C13006
[a] Cohort 1: patients enrolled in Cohort 1 were randomized to blinded induction treatment with vedolizumab or placebo
[b] Cohort 2: patients enrolled in Cohort 2 received open-label vedolizumab induction treatment

Finally, as in the Induction Study, a post hoc subgroup analysis including only patients meeting the US protocol criteria was completed. The number of patients meeting US Protocol criteria across the placebo, vedolizumab Q8W and vedolizumab Q4W treatment arms was comparable (54, 59, and 56, respectively). The clinical remission rates were comparable across subgroups and the treatment difference relative to placebo in the patients who met US protocol criteria was higher. These results are summarized in Table 28 below.

Table 28: Clinical Remission at Week 52 – Subgroup Analysis Based on the US Protocol Criteria

Clinical Remission[a]	Placebo N = 126	VDZ 300 mg Q8W N = 122	VDZ 300 mg Q4W N = 125
US Protocol Criteria Met	54	59	56
Number (%) achieving response	3 (5.6)	21 (35.6)	23 (41.1)
95% CI	(1.2, 15.4)	(23.6, 49.1)	(28.1, 55.0)
Difference from placebo (95% CI)		30.0 (11.7, 46.9)	35.5 (17.2, 51.9)
US Protocol Not Criteria Met	72	63	69
Number (%) achieving response	17 (23.6)	30 (47.6)	33 (47.8)
95% CI	(13.8, 33.4)	(35.3, 60.0)	(36.0, 59.6)
Difference from placebo (95% CI)		24.0 (8.2, 29.8)	24.2 (8.9, 39.5)

Source: Table 38.3.1.1D of response to questions clinical august 8 2013, page 28
[a] Clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point.
Confidence intervals for categorical data with numerators less than or equal to five are from the exact method, otherwise from the normal approximation.

A number of additional subgroup analyses on the primary efficacy endpoint were performed, and the results were consistent across a variety of subpopulations, including age, gender, race, baseline disease characteristics, and geographic region. Results favored vedolizumab over placebo.

Reviewer comments: The results were internally consistent across a variety of subgroups, including age, gender, race, duration of disease, geographic region, and

baseline disease activity, as well as anti-TNF users and failures. While the study was not powered for key subgroup analyses, because they were consistent with the overall results, this reviewer feels they can generally be believed. When analyzed separately, patients entering the Maintenance Study from both Cohort 1 and Cohort 2 achieved significantly higher proportion of clinical remission in the vedolizumab dosing groups than placebo. There was a numerically lower remission rate in patients who entered the Maintenance Study from Cohort 2; however, the study was not powered for this assessment, and all subgroups showed consistent results. This reviewer feels these results are consistent.

6.1.5 Analysis of Secondary Endpoints(s)

Induction Study

The secondary endpoints from the C13006 Induction Study are listed in the order they were tested:

- The proportion of patients who achieved clinical remission at Week 6.
- The proportion of patients with mucosal healing at Week 6.

The primary analysis population for both secondary endpoints was the Induction Study ITT population. The secondary endpoints were designed to support the following indications proposed by the applicant:

- "Reducing signs and symptoms, **inducing** and maintaining clinical response and **remission, and mucosal healing**, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist."

Clinical Remission

Based on the prespecified definition, patients in the vedolizumab treatment group achieved a significantly higher proportion of clinical remission at week 6 compared to patients in the placebo arm. Thirty-eight patients (16.9%) in the vedolizumab group achieved clinical remission, compared to 8 patients (5.4%) in the placebo group. A post hoc analysis was completed using an alternate definition of clinical remission which is described in 6.1.4 Analysis of Primary Endpoint for the Maintenance Study. When using the more stringent definition, vedolizumab did not induce clinical remission in a significantly larger proportion of patients at Week 6. The results are provided in Table 29 below.

Table 29: Clinical Remission at Week 6 using the applicant and more stringent definitions for clinical remission

Analysis Set	Placebo	VDZ 300 mg	Difference (VDZ – placebo)	p-value
ITT	8/149 (5.4)	38/225 (16.9)	11.5	0.0009
ITT – more stringent clinical remission definition	4/149 (2.7)	10/225 (4.4)	1.8	0.3728

Source: Clinical Study Report C13006 and Report on Supplemental Efficacy Analyses Requested by the FDA for C13006

Reviewer Comments: Patients in the vedolizumab treatment group were significantly more likely to achieve clinical remission at Week 6. While the results are not statistically significant in the sensitivity analysis using the more stringent definition for clinical remission, the applicant's original definition was agreed upon prior to submission, and the results from this sensitivity analysis still favor vedolizumab.

Mucosal Healing

Mucosal Healing was defined by the applicant as a Mayo endoscopic subscore of ≤ 1 point, where endoscopy subscores are defined as:

Table 30: Endoscopy Subscore Definitions

Endoscopy Subscore	Definition
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)

Source: Clinical study Report C13006

Based on the study data, 40.9% of patients in the vedolizumab treatment group achieved mucosal healing, compared with 24.8% of patients receiving placebo, a 16,1% treatment difference (p = 0.0012). When looking only at the subset of patients who had an endoscopy subscore of 0, however, the results are less clear. Eleven patients (4.9%) in the vedolizumab arm achieved an endoscopy subscore of 0 by Week 6, compared to 6 (4.0%) in the placebo arm. However, as stated before, the study was not powered for this analysis and results are only exploratory.

Reviewer Comments: The Division requested histological assessments from Phase 3 studies to better assess the mucosal healing endpoint. However, these were not collected in the clinical database in Study C13006, however. Given the lack of histological data, this reviewer believes these results can support only a claim of improved "endoscopic appearance of the mucosa".

Maintenance Study

The secondary endpoints for the C13006 Maintenance Study are listed in the order they were tested:

- The proportion of patients with a durable clinical response
- The proportion of patients with mucosal healing at Week 52
- The proportion of patients with durable clinical remission
- The proportion of patients achieving corticosteroid free clinical remission

The primary analysis population for all secondary endpoints was the Maintenance Study ITT population. The secondary endpoints were designed to support the following indications proposed by the applicant:

- Reducing signs and symptoms, inducing and **maintaining clinical response** and remission, and **mucosal healing, and achieving corticosteroid-free remission** in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.

Durable Clinical Response

The maintenance study was not limited to patients in remission at Week 6, rather it included all patients who demonstrated clinical response at the end of the Induction Phase. Durable clinical response was defined by the applicant as the proportion of patients in clinical response at Weeks 6 and 52 and thus all patients randomized in the Maintenance Study who were in clinical response at Week 52 met this endpoint. A significantly higher proportion of vedolizumab treated patients in both dosing regimens were in clinical response at Week 52 compared with patients who received placebo ($p < 0.0001$).

Table 31: Durable Clinical Response – Maintenance Study ITT population

Durable Clinical Response[a]	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving durable clinical response	30 (23.8)	69 (56.6)	65 (52.0)
95% CI	(16.4, 31.2)	(47.8, 65.4)	(43.2, 60.8)
Difference from placebo[b]		32.8	28.5
95% CI for difference from placebo		(20.8, 44.7)	(16.7, 40.3)
P value for difference from placebo[c]		< 0.0001	< 0.0001

Source: Clinical Study Report C13006, Table 14.3.1.4AM

[a] Durable clinical response is defined as reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1point or absolute rectal bleeding subscore of ≤ 1 point at both Weeks 6 and 52

[b] Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI

[c] P values are based on the CMH chi-square test, with 3 stratification factors: concomitant use of oral corticosteroids, previous exposure to TNFα antagonist or concomitant immunomodulator use, and enrollment in Cohort 1 or 2 in the Induction Phase

Reviewer comments: This data could support the claim of maintenance of clinical response, however, the clinical relevance of the term "durable" is unclear.

Durable Clinical Remission

The secondary endpoint of durable clinical remission, however, evaluated only those patients in clinical remission at weeks 6 and 52. Eleven patients (8.7%) in the placebo group met this secondary endpoint, compared with 25 (20.5%) in the vedolizumab Q8W group and 30 (24.0%) in the vedolizumab Q4W group. The applicant's results were statistically significant for both dosing regimens, p = 0.0079 and p = 0.00009 for Q8W and Q4W, respectively.

Table 32: Durable Clinical Remission – Maintenance Study ITT Population

Durable Clinical Remission[a]	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving durable clinical response	11 (8.7)	25 (20.5)	30 (24.0)
95% CI	(3.8, 13.7)	(13.3, 27.7)	(16.5, 31.5)
Difference from placebo[b]		11.8	15.3
95% CI for difference from placebo[c]		(3.1, 20.5)	(6.2, 24.4)
P value for difference from placebo		0.0079	0.0009

Source: Clinical Study Report C13006, Table 14.3.1.7AM

[a] Durable clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore of > 1 point at both Weeks 6 and 52

[b] Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI

[c] P values are based on the CMH chi-square test, with 3 stratification factors: concomitant use of oral corticosteroids, previous exposure to TNFα antagonist or concomitant immunomodulator use, and enrollment in Cohort 1 or 2 in the Induction Phase

Reviewer comments: These results would support the claim of maintenance of remission; however the clinical relevance of the term "durable" is unclear, particularly given the lack of a requirement for remission at any time points between weeks 6 and 52.

Mucosal Healing

Mucosal healing at Week 52 was defined based on Mayo endoscopic subscore of ≤ 1 point, as in the Induction Study. According to the applicant, both dosing regimens provided a statistically significant benefit over placebo with regards to this endpoint (p < 0.0001). Specifically, there was a 32.0% and 36.3% treatment difference favoring vedolizumab (Q8W and Q4W, respectively) over placebo. When analyzing only patients who had an endoscopic subscore of 0, the results remain statistically significant. Specifically, there was a 20.0 and 24.9% treatment difference favoring vedolizumab (Q8W and Q4W, respectively) over placebo (p < 0.0001 for both treatment arms).

Table 33: Mucosal Healing at Week 52 – Maintenance Study ITT Population

Mucosal Healing[a]	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125
Number (%) achieving durable clinical response	25 (19.8)	63 (51.6)	70 (56.0)
95% CI	(12.9, 26.8)	(42.8, 60.5)	(47.3, 64.7)
Difference from placebo[b]		32.0	36.3
95% CI for difference from placebo		(20.3, 43.8)	(24.4, 48.3)
P value for difference from placebo[c]		< 0.0001	< 0.0001

Source: Clinical Study Report C13006, Table 14.3.1.6AM

[a] Mucosal healing is defined as Mayo endoscopic subscore of ≤ 1

[b] Difference and 95% CI: adjusted percent vedolizumab – adjusted percent placebo and its 95% CI

[c] P values are based on the CMH chi-square test, with 3 stratification factors: concomitant use of oral corticosteroids, previous exposure to TNFα antagonist or concomitant immunomodulator use, and enrollment in Cohort 1 or 2 in the Induction Phase

Reviewer comments: The Division requested histological assessments from Phase 3 studies, if available, but these were not collected in the clinical database in Study C13006. Given the lack of histological data, these results can support only a claim of improved "endoscopic appearance of the mucosa". Given the consistent results when assessing the subset of patients with an endoscopic subscore of 0, this reviewer believes the applicant has demonstrated that vedolizumab improves the endoscopic appearance of the mucosa and that this finding may have clinical relevance to practitioners.

Corticosteroid-Free Remission

Based on the prespecified corticosteroid-free remission, a significantly higher proportion of patients from each of the vedolizumab arms were in clinical remission and on no corticosteroids at Week 52 than from the placebo group ($p = 0.0120$ for Q8W; $p < 0.0001$ for Q4W). Approximately 58% of patients in the Maintenance ITT population were receiving corticosteroids at Week 6. Patients on corticosteroids at Week 6 were on an average of 20 mg prednisone EQ dose at baseline. A higher proportion of overall patients were corticosteroid-free at Week 52 from both vedolizumab arms (47% Q8W and 56% Q4W) than from the placebo group (28%).

The prespecified definition of corticosteroid-free remission did not specify a minimum duration of time over which a patient was required to be corticosteroid-free; however, those patients who achieved the prespecified corticosteroid-free remission at Week 52 were corticosteroid free for an average of 270 days (260 days placebo, 267 days Q8W, and 274 days Q4W) compared to approximately 100 days (110 days placebo, 97 days Q8W, and 94 days Q4W) for those who did not achieve this endpoint. In addition, two exploratory analyses were completed to analyze the proportion of patients who achieved corticosteroid-free remission and were corticosteroid-free for 90 days and 180 days prior to Week 52. The results from these three analyses are provided in Table 34 below.

Table 34: Corticosteroid-Free Remission – Maintenance ITT Population, Patients on Corticosteroids at Baseline

Analysis Set	Placebo N = 72	VDZ 300 mg Q8W N = 70	Difference (VDZ – placebo)	p-value	VDZ 300 mg Q4W N = 73	Difference (VDZ – placebo)	p-value
Corticosteroid-Free Remission[a]	10(13.9%)	22 (31.4%)	17.6%	0.0120	33 (45.2%)	31.4%	< 0.0001
Corticosteroid-Free Remission and Corticosteroid Free for 90 Days	10(13.9%)	21 (30.0%)	16.2%	0.0192	33 (45.2%)	31.4%	< 0.0001
Corticosteroid-Free Remission and Corticosteroid Free for 180 Days	8 (11.1%)	20 (28.6%)	17.5%	0.0082	31 (42.5%)	31.4%	< 0.0001

Source: Clinical Study Report C13006
[a] Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.

Reviewer comments: The secondary endpoint of corticosteroid-free remission requires that two separate states be met; patients must be corticosteroid free and in clinical remission. The applicant demonstrated that neither of these two states (i.e., clinical remission or corticosteroid free) independently drove the overall claim, as a higher proportion of patients in the vedolizumab arms met each of these states individually.

The prespecified definition for corticosteroid-free remission does not define a pre-specified minimum duration of time over which a patient is required to be corticosteroid-free, which is necessary to demonstrate the clinical relevance of the endpoint. Patients who met this endpoint were corticosteroid free for an average of 260 days. In addition, the two exploratory analyses predefine a minimum duration of time for which patients must be corticosteroid-free (i.e., 90 and 180 days). The results are consistent with those of the prespecified secondary endpoint and showed statistically significant treatment differences from placebo in each of the dosing regimens and for both the 90- and 180-day endpoint. Achieving 3-6 months corticosteroid-free for patients with UC appears clinically meaningful and may be important information for the clinician. While the prespecified secondary endpoint did not specify a time period, the supportive evidence from exploratory endpoints and post hoc data are all supportive and consistent. However, the potential labeling claim should provide specific information about timing (e.g., 3-6 month corticosteroid free remission).

6.1.6 Other Endpoints

The exploratory endpoints analyzed by the applicant are not proposed to support any labeling claims and are thus not presented in detail in this review. Exploratory endpoints of particular relevance to the review of this application included the subgroup

analyses of patients considered TNFα failures, as well as the analysis of the subgroup of patients who achieved corticosteroid-free remission and were specifically corticosteroid free for 90 days and 180 days prior to Week 52. These exploratory endpoints are discussed in Sections 6.1.3 and 6.1.4, respectively. A brief summary of the other exploratory endpoints analyzed by the applicant is provided below.

Exploratory endpoints in the Induction and Maintenance Study included a number of exploratory subgroup analyses. Key endpoints were analyzed by treatment arm in patients with prior treatment failures, based on a patient's worst prior treatment failure (i.e., corticosteroid failure only, immunomodulator failure, anti-TNF failure). In both the Induction and Maintenance Studies, the results favored vedolizumab, though the 95% CIs included zero for clinical response at Week 6 in the immunomodulator failure group, and for clinical remission at Week 52 in the corticosteroid failure only group. These results are shown in Table 35 and Table 36 below.

Table 35: Week 6 Clinical Response by Worst Prior Treatment Failure

Worst Prior Treatment Failure	Corticosteroid Failure Only		Immunomodulator Failure		Anti-TNF Failure	
	PLA N = 25	VDZ N = 42	PLA N = 55	VDZ N = 96	PLA N = 63	VDZ N = 82
Number (%) achieving clinical response	5 (20.0)	25 (59.5)	19 (34.5)	47 (49.0)	13 (20.6)	32 (39.0)
95% CI	(6.8, 40.7)	(43.3, 74.4)	(22.0, 47.1)	39.0, 59.0)	(10.6, 30.6)	(28.5, 49.6)
Difference from placebo		**39.5**		**14.4**		**18.4**
95% CI for difference from placebo		(15.3, 60.6)		(-1.6, 30.5)		(3.9, 32.9)

Source: Clinical Study Report C13006, Table 14.3.1.12A

Table 36: Week 52 Clinical Remission by Worst Prior Treatment Failure

Worst Prior Treatment Failure	Placebo	Vedolizumab 300 mg Q8W	Vedolizumab 300 mg Q4W
Any prior anti-TNF Failure	**38**	**43**	**40**
Number (%) achieving response	2 (5.3)	16 (37.2)	14 (35.0)
Difference from placebo		31.9	29.7
95% CI for difference from placebo		(10.3, 51.4)	(7.4, 49.4)
Prior Immunomodulator Failure	**61**	**56**	**60**
Number (%) achieving response	11 (18.0)	25 (44.6)	30 (50.0)
Difference from placebo		26.6	32.0
95% CI for difference from placebo		(10.4, 42.8)	(16.1, 47.9)
Prior Corticosteroid Failure Only	**26**	**19**	**25**
Number (%) achieving response	7 (26.9)	8 (42.1)	12 (48.0)
Difference from placebo		15.2	21.1
95% CI for difference from placebo		(-12.8, 43.2)	(-4.9, 47.0)

Source: Clinical Study Report C13006, Table 14.3.1.14AM

Similarly, subgroup analyses were performed looking separately at patients with and without concomitant immunomodulator use. The vedolizumab groups performed better than placebo in these subgroup analyses looking at both clinical response at Week 6 and clinical remission at Week 52. No difference was seen in response rates between patients with and without concomitant immunomodulators. These results are shown in Table 37 and Table 38 below.

Table 37: Clinical Response at Week 6 in Patients with and without concomitant immunomodulator use

Endpoint	Patients With Concomitant Immunomodulator Use		Patients Without Concomitant Immunomodulator Use	
	PLA N = 44	VDZ N = 75	PLA N = 105	VDZ N = 150
Number (%) achieving clinical response	15 (34.1)	40 (53.3)	23 (21.9)	66 (44.0)
95% CI	(20.1, 48.1)	(42.0, 64.6)	(14.0, 29.8))	(36.1, 51.9)
Difference from placebo		**19.2**		**22.1**
95% CI for difference from placebo		(1.3, 37.2)		(10.9, 33.3)

Source: Clinical Study Report C13006, Table 22 page 136

Table 38: Clinical Remission at Week 52 in Patients with and without concomitant immunomodulator use

Endpoint	Patients With Concomitant Immunomodulator Use			Patients Without Concomitant Immunomodulator Use		
	Placebo	VDZ 300 mg Q8W	VDZ 300 mg Q4W	Placebo	VDZ 300 mg Q8W	VDZ 300 mg Q4W
N	51	43	45	75	79	80
Number (%) achieving response	10 (19.6)	19 (44.2)	21 (46.7)	10 (13.3)	32 (40.5)	35 (43.8)
Difference from placebo (95%CI)		24.6	27.1		27.2	30.4
95% CI for difference from placebo		(6.2, 43.0)	(8.9, 45.3)		(13.9, 40.5)	(17.1, 43.7)

Source: Clinical Study Report C13006, Table 60 page 214

Reviewer comments: The sample sizes for the subgroup analyses were small, so it is not unexpected that some of the 95% CIs included zero (i.e., clinical response at Week 6 in immunomodulator failures and clinical remission at week 52 in corticosteroid failures). The results for individual subgroups favored vedolizumab and were consistent with their primary endpoint results, so this reviewer believes the results indicate that vedolizumab is effective in these subgroups. There was no clear difference in benefit based on patients' worst prior treatment failure. Corticosteroid only failures appeared to show slightly more benefit in the Induction Study but less benefit in the Maintenance Study. The small numbers make any comparison between these groups difficult. There

did not appear to be any clinical benefit to the use of concomitant immunomodulators, as patients appeared to respond similarly with or without their use.

In addition, the applicant analyzed a number of exploratory endpoints, including patient reported outcomes (i.e., IBDQ score, SF-36, EQ-5D), fecal calprotectin, and time to disease worsening, time to treatment failure, and reduction in oral corticosteroid use. Of note, the applicant compared delayed clinical response rates by partial Mayo score in patients who did not achieve clinical response at Week 6. Specifically, patients who received vedolizumab during the Induction Phase but did not respond at Week 6 were assigned to continue vedolizumab Q4W during the Maintenance Phase. These patients were compared to placebo patients who had not responded at Week 6 and continued treatment on placebo in the Maintenance Phase. In a post hoc analysis, the response rate in the patients receiving vedolizumab was higher than for placebo patients at both Week 10 and Week 14. These endpoints were exploratory in nature, however, and would require independent validation in a well-controlled trial designed to assess these endpoints.

Reviewer Comment: As noted above, these endpoints are exploratory in nature and would not support a (b) (4) *without independent validation in a well-controlled trial designed to specifically assess these endpoints. Furthermore, the Agency's Study Endpoint and Labeling Development (SEALD) Team has determined that the items and domains of the Inflammatory Bowel Disease Questionnaire (IBDQ) are not appropriate, comprehensive, and interpretable relative to its intended use as a measure of health-related quality of life* (b) (4) *In addition, fecal calprotectin is not a validated surrogate endpoint for clinical outcomes in UC* (b) (4)

6.1.7 Subpopulations

The results for the primary efficacy endpoint for the C13006 Induction Study and Maintenance Study were consistent across a variety of subpopulations, including age, gender, race, baseline disease characteristics, and geographic region. Results favored vedolizumab over placebo. Figure 5 and Figure 6 below provide the risk difference and 95% confidence interval for subgroup analyses of clinical response at Week 6 and clinical remission at Week 52 in the vedolizumab Q8W group vs placebo, respectively.

Figure 5: Subgroup Analyses of Clinical Response at Week 6 - Induction Study ITT Population

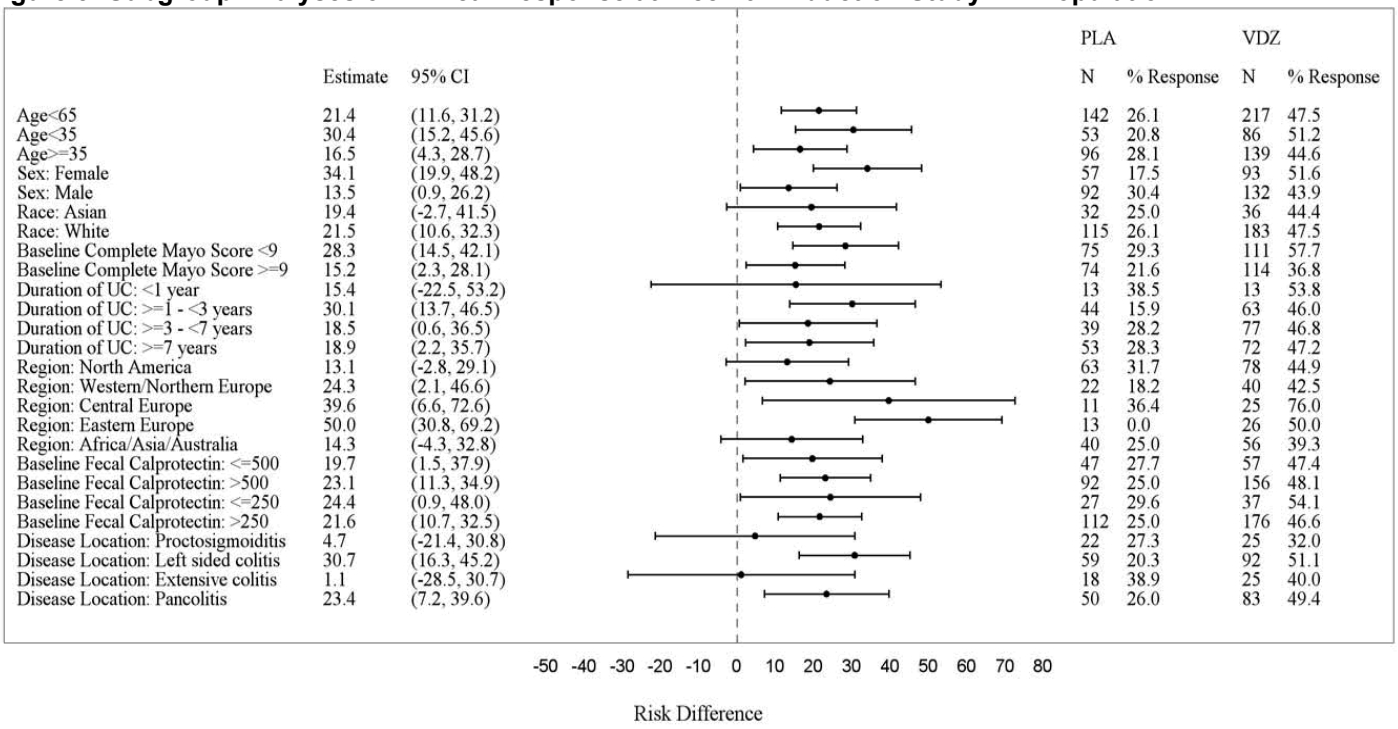

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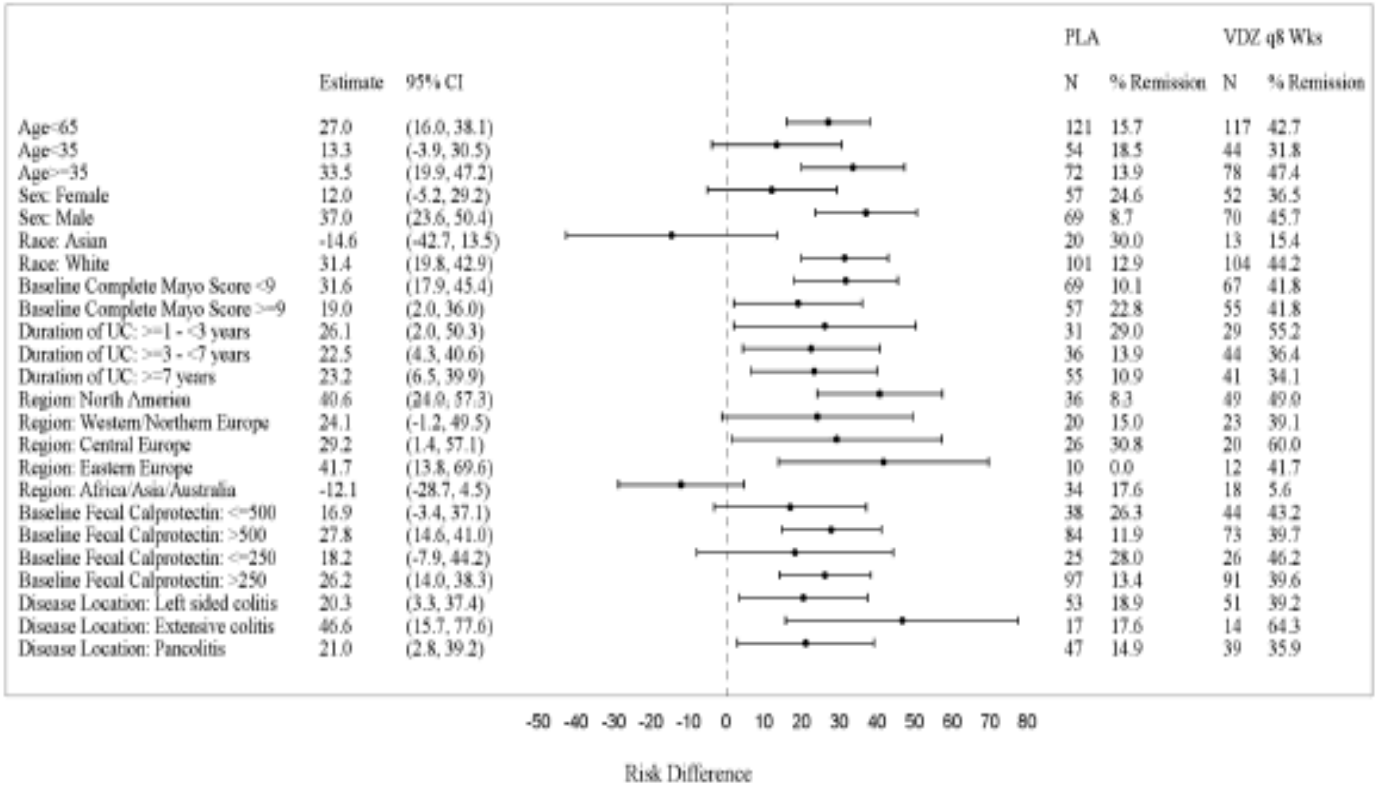
Figure 6:Subgroup Analyses of Clinical Remission at Week 52 for VDZ Q8W vs Placebo - Maintenance Study ITT Population



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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The selection of a 300 mg vedolizumab dose for Study C13006 was based on information from a number of sources, including dose response data from phase 2 studies (M200-022 and C13002), $\alpha_4\beta_7$ binding saturation data, PK/PD modeling, and suppression of HAHA formation. In phase 2 clinical studies in UC and CD patients (M200-22 and L299-016), the Applicant observed clinical remission at a dose where a near complete $\alpha_4\beta_7$ receptor blockade (>96%) was achieved within one hour after dose. The Applicant subsequently selected a dose of 300 mg (roughly equivalent to 4 mg/kg for a 75 kg subject) for the phase 3 studies in order to achieve sustained blockade of the $\alpha_4\beta_7$ receptors.

The final dosing recommendations for vedolizumab are a dose of 300 mg administered as an IV infusion over 30 minutes at Week 0, Week 2, Week 6, and Q8W thereafter. These dosing recommendations are based on data from C13006, specifically:

- 300 mg vedolizumab administered at Week 0 and Week 2 is effective in inducing clinical response and remission at 6 weeks.

- Both the vedolizumab 300 mg Q8W and Q4W dosing regimens were effective in maintaining clinical remission and response at 52 weeks.

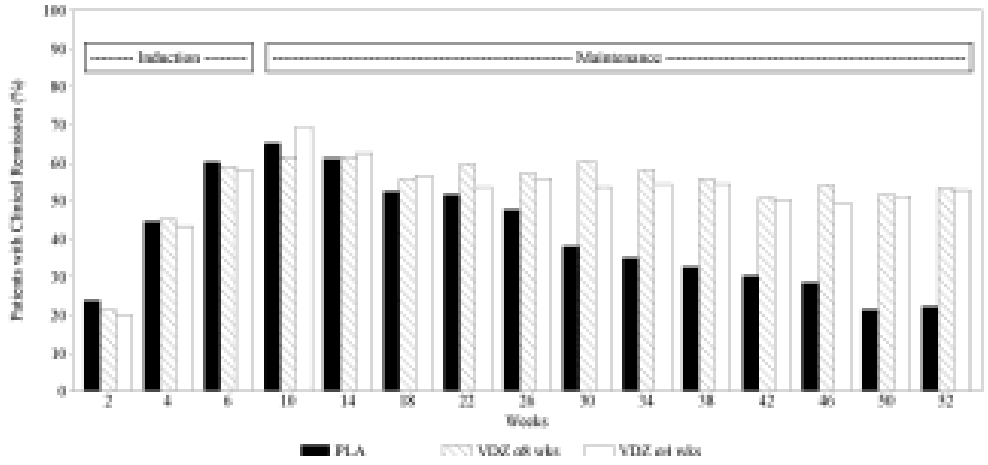
The Applicant recommends that if clinical response is not achieved by Week 6, or if patients lose response when dosed Q8W, dosing Q4W may be considered. The Applicant makes this recommendation based on PK data (vedolizumab trough data and PK modeling from Phase 3 studies) as well as information derived from Studies C13006 and C13008. Thirty-two patients in the vedolizumab Q8W treatment arm of the Maintenance Phase of C13006 withdrew prematurely due to lack of efficacy and switched to vedolizumab Q4W dosing in Study C13008. The clinical remission rate for these patients was 6.0% (2/32) at Week 0 based on partial Mayo and increased to 25.0% (8/32) at Weeks 28 and 52. These results must be considered with caution, however, given the small numbers and open-label design of study C13008.

Reviewer comments: Exploring lower doses in phase 2 studies may have helped to better characterize the exposure response relationship, however the clinical data supports the efficacy of vedolizumab 300 mg Q8W and Q4W for the maintenance of clinical remission and response. While both doses are effective, it is appropriate to treat with the lowest effective dose. An increase in dosing frequency for patients who fail to achieve clinical response by Week 6 was not formally studied as part of the applicant's Phase 3 program. Furthermore, Study C13006 was not powered to compare the Q4W and Q8W doses. Please see the Clinical Pharmacology Review for additional details on dose-response and dose selection.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Data from Study C13006 demonstrates the efficacy of vedolizumab at 52 weeks of treatment, as described in sections 6.1.4 and 6.1.5. It is difficult to comment on whether the therapeutic activity achieved was consistently sustained throughout the 52 week period, without endpoints including time periods throughout the Maintenance Phase. The applicant summarized clinical remission rates by study visit, based on partial Mayo score, however. The number of patients with clinical remission appeared to remain stable for vedolizumab treated patients through Week 52, while the number of placebo patients in clinical remission declined steadily from Week 10 through Week 52. This is shown in Figure 7 below.

Figure 7: Clinical Remission by Study Visit, Based on Partial Mayo Score – Maintenance Study ITT Population



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The secondary Maintenance Study endpoints of durable clinical response and durable clinical remission considered only response/remission at Weeks 6 and 52 and thus provide little additional information on whether treatment benefits were consistently sustained throughout the 52-week duration of the trial. Data from exploratory endpoints, such as the proportion of patients at Week 52 who are in clinical remission and have been corticosteroid-free for 90 days and 180 days suggest that benefit was sustained throughout the Maintenance Phase.

The persistence of efficacy beyond 52 weeks was assessed by integrating data from C13006 and the open-label extension study C13008. Efficacy was summarized by partial Mayo score at approximately 6-month intervals in C13008. The changes from baseline in partial Mayo score beyond 52 weeks showed sustained decreases in partial Mayo from baseline, suggesting persistence of efficacy. These results must be considered with caution, however, given the open-label design of the study, potential confounders, and lack of adjustment for multiplicity in the trial.

Tolerance effects were also assessed through the exploratory endpoints analyzing time to disease worsening and time to treatment failure, and no evidence of tolerance was seen. These endpoints were exploratory, however, and should be considered with caution. Persistent HAHA titers were seen in a small number of patients and were associated with decreases in the serum concentration of vedolizumab (in C13006, 23 of 620 patients were HAHA positive on study drug). It is difficult to draw any conclusions regarding the impact of this on efficacy, given the small number of patients.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues/analyses.

7 Review of Safety

Safety Summary

Overall, the safety profile of vedolizumab was adequately characterized during the clinical development program. A total of 3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as of March 14, 2013, the cut-off date for inclusion of safety data in the BLA. This included 1004 UC and CD patients who had received 24 or more infusions of vedolizumab with 4-weeks of follow-up.

In Clinical Trial C13006, the rates of adverse events were similar in the ITT populations, with 84% of patients in the placebo arm having any adverse event, compared to 82% and 81% in the Q8W and Q4W arms, respectively. More patients in the placebo-ITT arm reported a serious adverse event (16%) than in either of the vedolizumab-ITT arms (Q8W 8%, Q4W 9%). Similarly, a greater proportion of patients discontinued treatment due to adverse events in both placebo arms (placebo-ITT 12%, placebo non-ITT 11%) than in the combined vedolizumab group (6%). When combining results from the UC and CD populations (Studies C13006 and C13007) the results were similar. The proportion of patients with at least 1 adverse event was 84%, 78% and 84% in the ITT placebo, non-ITT placebo, and combined vedolizumab groups, respectively.

Serious adverse events (SAEs) were reported in 19% of patients receiving vedolizumab throughout, compared to 13% of patients who received placebo only. Serious infection AEs and those considered drug-related occurred with similar frequency between the vedolizumab and placebo groups (serious infection AE 4% and 3% respectively, and drug-related SAE 3% and 2%, respectively). The most frequently reported SAEs (≥ 1% of the VDZ/VDZ population) were related to underlying IBD and included Crohn's disease, ulcerative colitis, and anal abscess. The higher proportion of patients reporting at least 1 SAE in the vedolizumab group was largely driven by SAE reporting in C13007. There was a higher overall rate of SAEs in Trial C13007 for Crohn's disease, with 199 (24%) of patients in the combined vedolizumab group reporting at least 1 SAE, compared to 23 (16%) in the non-ITT placebo group.

Adverse events leading to clinical trial discontinuation was similar between the placebo groups and combined vedolizumab groups. The most common AEs resulting in study discontinuation from the combined group were ulcerative colitis and Crohn's disease.

One death (0.3%) occurred during the controlled clinical trial period in a patient receiving placebo, compared with 5 deaths (0.3%) in patients receiving vedolizumab.

An additional 7 patients died in the open-label extension trial C13008, 3 with UC and 4 with CD. The events leading to death among the UC patients were respiratory failure, cerebrovascular accident, and pulmonary embolism. None of these events were determined to be related to study drug. Among the CD patients, traumatic intracranial hemorrhage, hepatic neoplasm, suicide, and sepsis led to patient deaths. Again, none of these deaths were determined to be related to the study drug, as per the clinical reviewer assessment.

The proportion of patients with at least 1 adverse event in studies C13006 and C13007 was 84%, 78% and 84% in the ITT placebo, non-ITT placebo, and combined vedolizumab group, respectively. The most commonly reported adverse events which occurred more commonly in the vedolizumab treated patients were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, and cough. All of these adverse events occurred in at least 5% of the combined vedolizumab group. The rates of common adverse events, when considered by patient-years, were similar between the combined vedolizumab group and the non-ITT placebo group. The frequency of nonserious AEs, categorized as "severe" was also similar across the 3 treatment groups in Studies C13006 and C13007. Thirteen percent of patients in the ITT placebo reported severe AEs, compared to 14% in the non-ITT placebo and 15% in the combined vedolizumab group. Crohn's disease, abdominal pain, and ulcerative colitis were the only AEs categorized as severe which were reported in at least 1% of the combined vedolizumab group, and these occurred at similar frequencies in the 3 treatment groups.

A higher proportion of patients in vedolizumab treated groups reported 1 or more infectious AE, than in the placebo groups. In both the UC and CD populations, infections involving the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection) were the most commonly reported infection and occurred with greater frequency in vedolizumab treated patients than placebo. There was no increase in serious infection related AEs seen. Oronasal-associated lymphocytes show primary α4β7 expression, suggesting the MAdCAM-1 interactions may have a role in nasal infections. The greater frequency of upper respiratory tract infections is consistent with vedolizumab's mechanism of action in inhibiting the α4β7-MAdCAM-1 interaction. There is the potential that this represents an off target event, however, and this should continue to be monitored in the post-marketing setting. Furthermore, labeling language indicating that vedolizumab is (b) (4) may be misleading.

Serious infections were reported in both controlled and open-label trials. Serious infections were more common in CD patients. In Study C13007, serious infections were reported in 5 (3%), 4 (3%), and 45 (6%) of patients in the VDZ/PLA, PLA/PLA, and VDZ/VDZ groups, respectively. Serious infections were reported by 20 patients in C13006 and at a similar frequency across dose groups (3% VDZ/PLA; 3% PLA/PLA; 2% VDZ/VDZ). Anal abscesses were the most frequently reported serious AE among

CD patients, and the frequency was highest in the non-ITT vedolizumab group. Other serious adverse events reported included sepsis, tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegalovirus colitis.

One case of potential drug related liver toxicity was reported in Study C13006 and a second case with the 120-day safety update. Case report information provided for both indicate a possible drug or autoimmune etiology. Both patients were treated with corticosteroids and study drug was discontinued, complicating determination of etiology. Additional information was requested of the applicant, both on these two cases and any additional cases of hepatitis or liver injury where drug induced or autoimmune hepatitis were considered in the differential was requested. This information is pending at the time of this review. An addendum will be provided with pertinent information from the response to information request and following further internal discussions.

No apparent signals for increased risk for an adverse event or any type of adverse event when assessing AEs by a variety of demographic factors was seen, including age, sex, geographic region, and prior IBD treatments. Patients with previous TNFα use had a higher overall rate of AEs, however, the AE rates were similar between treatment groups in this subset.

Since 2007, the vedolizumab clinical development program included a Risk Assessment and Minimization for PML (RAMP) program. The RAMP program was thorough, and no cases of PML were identified through the 120 day safety data cutoff. This included 1004 patients exposed to 24 or more vedolizumab infusions with 4-weeks of follow up and approximately 80% of whom received prior immunosuppressant therapy. Less than 1% of patients tested positive for JC viremia; JCV antibody testing was not included in the RAMP program.

7.1 Methods

A total of 3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as of June 27, 2013. This included 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. Safety data for vedolizumab will be presented focusing on the comparative safety data in UC patients (Clinical Trial C13006), combined comparative safety data in UC and CD patients (Clinical Trials C13006 and C13007,), and long term safety data (Clinical Trial C13008). These are described in detail below, and the safety populations for these analyses are defined in Table 39.

Table 39: Safety Populations and Definitions

Safety Population	Definition
Non-ITT placebo	patients who received continuous double-blind placebo throughout the entire 52-week trial (C13006)
Combined vedolizumab	patients who responded to vedolizumab 300mg treatment during induction and were randomized to Q8W or Q4W vedolizumab 300mg (ITT vedolizumab), as well as those patients who did not respond to vedolizumab during the induction phase and received open label vedolizumab 300mg Q4W (non-ITT vedolizumab) during the maintenance phase.
ITT vedolizumab	*patients who responded to vedolizumab 300mg treatment during induction and were randomized to Q8W or Q4W vedolizumab 300mg*
Non-ITT vedolizumab	*patients who did not respond to vedolizumab during the induction phase and received open label vedolizumab 300mg Q4W during the maintenance phase*
ITT-placebo	patients who received vedolizumab during induction and were randomized to receive placebo during the maintenance phase. The clinical meaningfulness of this group for safety comparisons is complicated by their vedolizumab exposure during induction (half-life of ~25 days), so this group will be presented separately from the non-ITT placebo group. The ITT-placebo group will also be included in the overall vedolizumab exposure groups.

UC Comparative Safety

To provide a comparative safety analysis in patients with UC, safety data from Clinical Trial C13006 will be presented and separated by treatment arms. The Maintenance Phase Safety Population includes safety data from all 895 patients enrolled in C13006 from Week 0 through clinical trial completion, including patients who discontinued prior to the Maintenance Phase of the trial. The maintenance ITT populations will be compared and includes patients who responded to vedolizumab during induction and were randomized to either vedolizumab every 4 weeks, vedolizumab every 8 weeks, or placebo for the Maintenance Phase. To augment these comparisons, the non-ITT placebo group and the combined vedolizumab group will also be compared.

UC and CD Comparative Safety

The focus of the UC and CD comparative safety evaluation is on comparing adverse events from the phase 3 placebo-controlled trials which included a 52-week induction and maintenance trial (C13006 and C13007). Clinical Trial C13011 was an induction trial only and will not be included unless specified. This safety population includes safety data from all patients enrolled in these trials from Week 0 through trial completion. The patients from Clinical Trials C13006 and C13007 are believed to be sufficiently similar that pooling of the data is appropriate and will increase the power to find any safety signals. In addition, these patients were exposed to vedolizumab at the proposed dose for licensure of 300 mg and are similar to patients who may receive this product in clinical practice. The focus of these comparisons is on the 1434 patients in the combined vedolizumab group and the 297 patients in the non-ITT placebo group. The non-ITT placebo and combined vedolizumab groups are particularly relevant, as

these patients stayed in the same treatment group throughout the 52 weeks, although some in the combined vedolizumab group received vedolizumab open label. An additional 279 patients received vedolizumab during induction and were randomized to receive placebo during the maintenance phase (ITT-placebo group).

Long-term Safety

The long-term UC and CD safety population focuses on safety data from Trial C13008, a long term extension study evaluating safety with continued vedolizumab in patients with UC or CD. This long-term safety population (N= 2243) includes both rollover patients (N=1822) and de novo patients (N=421). For patients who received vedolizumab in qualifying clinical trials and rolled into C13008, the frequency of AEs was analyzed across the originating trial and Trial C13008. For patients who received placebo during the previous trial, AEs were not counted during the time of placebo administration. For these patients and de novo patients, all AEs were summarized from the first dose of vedolizumab.

Exposure data and presentation of deaths and other specifically relevant AEs (i.e., PML) will use the entire safety population, controlled and uncontrolled studies in patients and healthy volunteers.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed primarily from Clinical Trials C13006 and C13007, and additional safety data was obtained from the ongoing open-label extension trial, C13008. See section 7.1 for additional details.

Table 40: Clinical Trials Used to Evaluate Safety

Clinical Trial ID	Trial Design/No. of Centers	Trial Population	Treatment Arms	Number of patients by treatment entered/completed	Safety Endpoints
C13006	Phase 3, randomized, placebo-controlled, double-blind, multicenter trial/211	Male or female patients, aged 18 – 80, with moderately to severely active Ulcerative Colitis	VDZ 300 mg or placebo at Weeks 0 and 2	VDZ: 746/703 Placebo: 149/135	AEs, PML symptom checklist, plasma JC virus testing, vital signs, stool samples, ECG results, laboratory results (including standard hematology, clinical chemistry, coagulation, and urinalysis) Immunogenicity: blood samples for HAHA assessment
			VDZ 300 mg Q4W or Q8W or placebo from week 6 until week 52	ITT VDZ Q4W: 125/84 Non-ITT VDZ Q4W: 373/135 VDZ Q8W: 122/77 ITT Placebo: 126/48 Non-ITT Placebo: 149/30	
C13007	Phase 3, randomized, placebo-controlled, double-blind, multicenter trial/285	Male or female patients, aged 18 – 80, with moderately to severely active Crohn's Disease	VDZ 300 mg or placebo at Weeks 0 and 2	VDZ: 968[a]/873 Placebo: 148/137	
			VDZ 300 mg Q4W or Q8W or placebo from week 6 until week 52	ITT VDZ Q4W: 154/82 Non-ITT VDZ Q4W: 506/163 VDZ Q8W: 154/73 ITT Placebo: 153/64 Non-ITT Placebo: 148/42	
C13008	Phase 3, open-label, long-term, safety extension trial/292	Male or female, aged 18 – 80, rolling over from previous qualifying VDZ studies. De novo patients were also enrolled but only included in safety analyses.	VDZ 300 mg Q4W	Total: 2243/1411	

[a] 1 patient withdrew before receiving a single dose

It should be noted that the clinical development program used three different formulations of drug product. Process A was (b) (4) and was studied in phase 1 and phase 2 trials. Process B was (b) (4), and Process C is a lyophilized formulation for infusion or injection. Bioequivalence between Processes B and C was demonstrated in healthy subjects in Study C13009. Table 41 below summarizes the formulations used in clinical development. All of these clinical trials/formulations were included in the overall exposure data presented by the applicant.

Table 41: Summary of Formulations Used During Clinical Development

		Number Dosed	
Trial (formulation[a])	Phase	Placebo	Vedolizumab
Healthy Subjects			
L297-007 (Process A)	1	5	14
C13001 (Process B)	1	10	39
C 13005 (Process B)	1	0	26
C13009 (Process B &C)	1	25	62
C13010 (Process C)	1	0	42
C13012 (Process C)	1	0	14
Ulcerative Colitis			
L297-005 (Process A)	1b/2a	5	9
L297-006 (Process A)	1b/2a	8	21
M200-021 (Process A)	1/2	6	24
M200-022 (Process A)	2	63	118
C13002 (Process B)	2	9	37
C13006 (Process C)	3	149	746
Crohn's Disease			
L299-016 (Process C)	2	58	127
C13007 (Process C)	3	148	967
C13011 (Process C)	3	207	209
Ulcerative Colitis and Crohn's Disease			
C13004 (Process B)	2	0	72
C13008 (Process C)	3		
Rollover patients		0	1822
De novo patients[b]		0	421

Source: Sponsor submission, Integrated Summary of Safety, pp 25-26
[a] Process A is (b) (4); Process B is (b) (4); Process C is a lyophilized formulation used for infusion or for injection
[b] De novo patients had not participated in a previous trial of vedolizumab

Reviewer Comments: All Phase 3 trials were conducted using Process C materials, and these are the focus of the safety evaluation. This is acceptable.

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) was used for coding all AEs. Specifically, AEs were coded and grouped into Preferred Term (PT), High Level Term (HLT), and System Organ Class (SOC), using MedDRA Version 14.0. Based on a FDA Investigators Rapid Review System (FIRRS) MeDRA term matching comparison looking at a random sample of 20% of AE terms and this reviewer's review of all AE coding (verbatim terms to dictionary terms), the AE data is adequately coded.

An adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not it was considered to be study drug related. This included any increase in severity or frequency of a preexisting condition. Signs and symptoms of IBD were only to be collected if they developed or worsened during the clinical trial. All AEs were categorized according to severity:

- mild: awareness of event but easily tolerated

- moderate: discomfort enough to cause some interference with usual activity
- severe: inability to carry out usual activity

In addition, the following causal relationship categories were used for all vedolizumab clinical trial AEs:

- related: there was a reasonable causal relationship between the study drug and the AE.
- unrelated: there was not a temporal relationship to study drug administration, or there was a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

The incidence of AEs was assessed in the combined UC and CD induction and induction/maintenance population by a number of subpopulations, including age, race, sex, baseline disease activity, weight at baseline, creatinine clearance, geographic region, prior use of TNFa, and use of baseline concomitant IBD medications.

Reviewer comment: The applicant's categorization of adverse events was adequate as assessed by this reviewer's comparison of verbatim terms to preferred terms as well as the FIRRS analysis. This reviewer notes some splitting of terms related to upper respiratory and nasopharyngeal tract infections. This is discussed further in section 7.4.1 below.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As discussed in Section 7.1, adverse event data were pooled across the 2 phase 3 controlled studies which included a Maintenance Trial (Trial C13006 in UC, and Trial C13007 in CD). The patients from these studies are believed to be sufficiently similar that pooling of the data is appropriate.

7.2 Adequacy of Safety Assessments

The safety of vedolizumab was assessed throughout the clinical development program, and clinical trials were overseen by independent data safety monitoring boards. Individual clinical trial protocols outlined safety monitoring and included assessment of AEs, serious AEs, and deaths, monitoring for PML, and the following specific safety related testing:

- Clinical laboratory data:
    - hematology: hematocrit, hemoglobin, platelets, white blood cell count, red blood cell count, absolute basophil count, absolute eosinophil count,

absolute lymphocyte count, absolute monocyte count, and absolute neutrophil count
    - clinical chemistry: albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, amylase, bicarbonate, BUN, calcium, creatinine, glucose, lipase, magnesium, phosphorus, total and direct bilirubin, total protein, sodium, potassium, and chloride
    - coagulation: prothrombin time and partial thromboplastin time
- Immunogenicity testing: Blood samples for human antihuman antibodies (HAHA) were obtained at protocol-specified visits to evaluate the potential immunogenicity of vedolizumab.
- JC Viremia: Blood samples for JC viremia were obtained.
- Vital Signs: Heart rate, respiratory rate, blood pressure, and temperature.
- Electrocardiogram: A 12-lead ECG was obtained at rest were obtained and any findings from ECGs collected after study drug administration were to be captured as AEs if there was a clinically significant change from baseline.

Importantly, since 2007, all patients enrolled in vedolizumab trials have been actively monitored for PML through the Risk Assessment and Minimization for PML (RAMP) program. This program included investigator and patient education, required screening prior to enrollment, frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. For example, prior to entering the trial, patients were administered a Subjective Checklist (see Table 42, below) including relevant neurologic signs and symptoms. Patients with one or more positive result at baseline were excluded from the clinical trial. The same Subjective Checklist was also administered at each visit prior to study drug administration and at the Final Safety visit. For any patients with 1 or more positive responses on the Subjective Checklist, an objective test (Objective Checklist) was to be administered by the investigator.

Table 42: Subjective Checklist

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Objective Checklist
	Yes	No		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				Test visual fields and ocular motility
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barre maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				Ask for spontaneous writing sample and observe finger to nose, heel to shin, and tandem gait.
5. Have you regularly been experiencing difficulty understanding others?				Ability to follow serial commands
6. Have you had persistent problems with your memory or thinking?				Recall of 3 objects over 1 minute with distraction; ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

Modified from sponsor's table Subjective PML checklist from IR response dated 2-18-11, page 44.

The Objective Checklist required the investigator to perform a specific neurological test for each positive symptom. Any positive finding on the Objective Checklist resulted in a referral to the site's study neurologist. If the site study neurologist was unable to exclude PML on the basis of history and neurological examination, the subject was referred for a brain MRI and the case is evaluated by the Independent Adjudication Committee (IAC) to undergo additional diagnostic testing and independent assessment. In addition, blood samples were obtained for JC viremia at screening, week 6, every 8 weeks thereafter, and at the week 52 visit or early termination visit (prior to dosing). If a subject had persistent JC virus, regardless of symptoms, the case was reviewed by the IAC.

Patients were not permitted to receive additional study drug until PML was excluded, and if a case of PML was confirmed, the subject could no longer receive study drug. In addition to this on study monitoring, all participants were to participate in a follow-up questionnaire administered via telephone at 6, 12, 18, and 24 months after the final dose of study drug.

Reviewer comments: Appropriate safety evaluations were performed as part of the drug development program. The RAMP program adequately assessed for signs and symptoms of PML in clinical trial participants in order to identify potential cases early.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The applicant's safety database exceeds the ICH E1A recommendations for drugs that are to be used chronically *(reference: ICH E1A Guidance "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf (accessed September 24, 2013)). Given the potential risk for PML with this class of agents, however, the applicant was recommended to provide a significantly larger safety database. The final recommendation from the Division was that a minimum of 900 patients should have received ≥ 24 infusions with 4 weeks post-infusion follow up, in order to provide a pre-approval assessment of PML risk in patients with UC and CD that would be adequate to take to Advisory Committee for consideration.

A total of 3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as of June 27, 2013. This included 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. Across all clinical studies, 2022 patients were exposed to vedolizumab for ≥ 6 months, 1418 patients for ≥ 12 months, 906 for ≥ 24 months, and 407 for ≥ 36 months. Patients were exposed to vedolizumab for a mean of 480.6 days in Phase 2 and 3 studies combined and for a mean of 532.0 days in phase 3 trials combined. Table 43 shows a summary of exposure to vedolizumab by months of exposure and number of infusions.

Table 43: Duration of Exposure to Vedolizumab by Months of Exposure and Number of Infusions (as of 27 June 2013)

Duration	Healthy Subjects	Ulcerative Colitis	Crohn's Disease	Total[a]
At least 1 dose[b]	197	1279	1850	3326
Months of exposure				
≥ 6	0	855	1167	2022
≥ 12	0	588	830	1418
≥ 18	0	485	677	1162
≥ 24	0	428	478	906
≥ 36	0	198	209	407
≥ 48	0	30	10	40
Number of infusions with 4-week follow-up				
≥ 1	193	1261	1826	3280
≥ 6	0	913	1283	2196
≥ 12	0	673	916	1589
≥ 18	0	498	730	1228
≥ 24	0	444	560	1004
≥ 36	0	254	278	532
≥ 48	0	63	53	116

Source: Applicant Submission, Integrated Summary of Safety, 120-day Safety Update, Tables 3-1 and 3-2
[a] Exposure from Studies C13013 and CPH-001 is not included
[b] Dose is defined as administration of any amount of vedolizumab in phase1/2 studies and as administration of ≥ 75% of volume in phase 3 studies

The Agency was particularly concerned about the impact of prior and concomitant immunosuppressant use and its potential impact on PML risk. Approximately 80% of patients from Phase 3 studies had prior immunosuppressant use (i.e., azathioprine and 6-mercaptopurine), and approximately 30% continued immunosuppressants during the trial. The US protocols did not allow concomitant immunosuppressant use beyond the Week 6 induction period. Outside the US, however, there were no restrictions on continued immunosuppressant use. The table below summarizes the number of vedolizumab infusions by prior and concomitant exposure to immunosuppressants. Because patients from the US were required to discontinue immunosuppressants by Week 6, they were classified as no concomitant immunosuppressant use.

Table 44: Vedolizumab Exposure by Concomitant Immunosuppressant[a] Use

Category	Number of Vedolizumab Infusions[b,c]				
	≥ 6 N = 2195	≥ 12 N = 1488	≥ 18 N = 1171	≥ 24 N = 903	≥ 36 N =415
Prior Immunosuppressant Use					
Yes	1757 (80)	1171 (79)	913 (78)	690 (76)	305 (73)
No	438 (20)	317 (21)	258 (22)	213 (24)	110 (27)
Concomitant Immunosuppressant Use[d]					
Yes	608 (28)	449 (30)	356 (30)	268 (30)	107 (26)
No	1587 (72)	1039 (70)	815 (70)	635 (70)	308 (74)

Source: Applicant Submission, Integrated Summary of Safety, Table 2-7
[a] Concomitant immunosuppressants included azathioprine and 6-mercaptopurine
[b] Includes patients from studies C13002, C13004, C13006, 13007, 13008, and 13011; healthy volunteers are not included
[c] Patients had a minimum of 4 weeks follow-up after the last infusion
[d] All US patients are classified as no concomitant immunosuppressant use

Of the patients outside the US categorized as using concomitant immunosuppressant, over half remained on concomitant immunosuppressants for over a year. Duration of concomitant immunosuppressant use is summarized in Table 45, below.

Table 45: Duration of Concomitant Immunosuppressant Use

Duration of Concomitant Immunosuppressants	Ulcerative Colitis N = 282	Crohn's Disease N = 468	Total N = 750
At least 1 dose, n (%)	282 (100)	468 (100)	750 (100)
Months of Exposure			
≥ 3	246 (87)	388 (83)	634 (85)
≥ 6	208 (74)	331 (71)	539 (72)
≥ 12	155 (55)	268 (57)	423 (56)
≥ 18	134 (48)	187 (40)	321 (43)
≥ 24	119 (42)	129 (28)	248 (33)
≥ 36	24 (9)	38 (8)	62 (8)
≥ 48	2 (<1)	1 (<1)	3 (<1)

Reviewer comments: The applicant provided adequate exposure data, based on the Division recommendations to adequately assess PML risk pre-approval. The difference between the number of patients with ≥ 24 months vedolizumab exposure (906) and the number of patients with ≥ 24 vedolizumab infusions (1004) can be explained by 2 reasons. Patients received 2 infusions during the first 2 weeks of induction phase, and patients in the every 4 week cohort received 13 infusions every 12 months.

7.2.2 Explorations for Dose Response

Please see section 6.1.8, Analysis of Clinical Information Relevant to Dosing Recommendations, as well as the Clinical Pharmacology and Pharmacometrics reviews for additional details and assessment of the exposure-response relationship.

The applicant selected 1 induction dose and 2 maintenance dosing regimens to explore in Phase 3 Studies. All patients received 300mg vedolizumab by intravenous infusion at weeks 0 and 2 for induction. During the maintenance phase, patients received 300 mg vedolizumab IV, either every 4 or every 8 weeks.

Exploration for safety dose-response was undertaken using data from the pivotal UC trial, C13006 and comparing the adverse events between the 3 Maintenance Trial ITT populations (i.e., placebo, vedolizumab Q8W, and vedolizumab Q4W), as these patients continued to receive blinded study drug throughout the maintenance phase. It is important to note, however, that the placebo ITT population received 2 vedolizumab infusions during induction before being randomized to placebo for the Maintenance Phase.

The adverse event rates were similar between dosing groups. Specifically, 84% of patients in the placebo-ITT group experienced one or more AE, compared to 82% and

81% in the Q8W and Q4W vedolizumab groups, respectively. Sixteen percent of patients in the placebo group had a serious adverse event and 12% had an adverse event resulting in discontinuation, compared to 8% and 6% in the Q8W vedolizumab group and 9% and 5% in the Q4W group.

When comparing adverse events by specific SOCs, there was no clear trend of higher AEs with the more frequent dosing regimen. Finally, no safety dose-response relationship was seen between dosing regimens for the most common AEs by PT. The results for the fifteen AEs with the highest rates in the combined vedolizumab group are summarized in Table 46, below.

Table 46: Common Adverse Events by Preferred Term in the Maintenance Trial ITT Population

	PLA N = 126 TPY = 83.7			VDZ Q8W N = 122 TPY = 95.4			VDZ Q4W N = 125 TP = 101.3		
Preferred Term, n (%)	n (%)	Events	Incidence Density[a]	n (%)	Events	Incidence Density	n (%)	Events	Incidence Density
Ulcerative colitis	29 (23)	29	0.346	15 (12)	17	0.178	18 (14)	23	0.227
Headache	15 (12)	22	0.263	16 (13)	24	0.252	17 (14)	45	0.444
Nasopharyngitis	15 (12)	20	0.239	19 (16)	22	0.231	18 (14)	26	0.257
Arthralgia	15 (12)	16	0.191	11 (9)	15	0.157	13 (10)	13	0.128
URI	13 (10)	19	0.227	12 (10)	17	0.178	12 (10)	17	0.168
Nausea	8 (6)	9	0.108	4 (3)	6	0.063	9 (7)	13	0.128
Cough	6 (5)	6	0.072	9 (7)	9	0.094	5 (4)	6	0.059
Anemia	5 (4)	5	0.060	5 (4)	5	0.052	5 (4)	5	0.049
Abdominal Pain	2 (2)	2	0.024	9 (7)	10	0.105	9(7)	16	0.158
Fatigue	5 (4)	5	0.060	5 (4)	5	0.052	4 (3)	10	0.099
Influenza	3 (2)	4	0.048	8 (7)	9	0.094	2 (2)	2	0.020
Vomiting	1 (<1)	1	0.012	0	0	0.000	6 (5)	7	0.069
Oropharyngeal Pain	1 (<1)	1	0.012	7 (6)	7	0.073	6 (5)	7	0.069
Bronchitis	7 (6)	7	0.084	7 (6)	7	0.073	6 (5)	7	0.069
Pyrexia	7 (6)	7	0.084	3 (2)	3	0.031	2 (2)	2	0.020

Source: Table modified from Table 75 in CSR for Clinical Trial C13006, pages 257-258.
Number of events: within the same preferred term, if the start and stop date of multiple events overlapped or start and stop date were the same, the term was counted as 1 event; if multiple events did not overlap, the term was counted as separate events
[a] incidence density is defined as the number of events divided by total person time in years, where days for person time is defined as (end of study date – first dose date [of induction] +1). The end of study date was the date of the last known dose of study therapy during the Maintenance Phase. For patients who did not participate in Trial C13008, the end date was the date of last known dose of study therapy plus 16 weeks.

Reviewer comment: As previously stated, the proportion of patients with AEs and serious AEs in the combined vedolizumab groups and non-ITT placebo group in Clinical Trial C13006 was similar. There was no clear trend of higher incidence of AEs with the more frequent dosing regimen. Given the high dropout rate in the Maintenance Phase, the incidence density was also considered. No clear trends are observed. There does not appear to be a dose-adverse event relationship.

7.2.3 Special Animal and/or In Vitro Testing

Due to the increased risk of PML with natalizumab, an integrin receptor antagonist, other products with similar mechanisms of action may also be at increased risk for this rare but serious demyelinating disease caused by reactivation of latent JC virus infection in the central nervous system (CNS). The applicant completed nonclinical studies aimed at characterizing the binding specificity and selective antagonism of vedolizumab in order to support that vedolizumab has a lower risk of causing PML than natalizumab.

Vedolizumab is a monoclonal antibody that selectively binds to α4β7 integrin, a glycoprotein present on the surface of leukocytes involved in GI mucosal immunity. The ligand of α4β7 integrin is mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is preferentially expressed on the endothelium of GI mucosa. The mechanism of action of vedolizumab is the inhibition of leukocyte migration to the GI mucosa and interaction with MAdCAM-1. Natalizumab, in contrast, binds to the α4 integrin subunit and thus binds both α4β7 and α4β1, which binds to the endothelial ligand vascular cell adhesion molecule-1 (VCAM-1). An in vitro study utilizing cell lines selectively expressing specific integrins showed that vedolizumab selectively binds to α4β7 and does not bind to α4β1 or αEβ7 integrin. This study also examined the selectivity of vedolizumab for inhibition of α4β7-mediated cell adhesion interactions and showed that vedolizumab inhibited α4β7-MAdCAM-1 and fibronectin and did not inhibit α4β7-VCAM-1, α4β1-VCAM-1, or α4β1-fibronectin-mediated adhesive interactions.

A decrease in immune surveillance of the CNS by T-lymphocytes is hypothesized to contribute to the development of PML. The sponsor conducted a study using an Experimental Autoimmune Encephalomyelitis (EAE) model in Rhesus monkeys (a model of multiple sclerosis; there is no animal model of PML) to assess the impact of vedolizumab and natalizumab on CNS immune surveillance. The results of this study showed that while natalizumab appeared to inhibit immune surveillance of the CNS, vedolizumab had no such effect. In addition, a 3-week comparative immunotoxicity study of natalizumab and vedolizumab was completed in Cynomolgus monkeys. Natalizumab caused a significant increase in lymphocyte populations (e.g., b-lymphocytes, t-helper lymphocytes, etc.), whereas there was no change in these populations in vedolizumab-treated monkeys.

The applicant proposes that their nonclinical data supports the specificity of vedolizumab and the use of vedolizumab does not carry the same increased risk of PML as natalizumab.

See nonclinical pharmacology/toxicology section 4.3 for routine animal and in vitro testing performed and the Nonclinical Review by Tamal Chakraborti, PhD, for additional details.

Reviewer comment: The nonclinical data supports the specificity of vedolizumab, however, the mechanism by which PML develops in patients administered integrin antagonist products is not completely understood. Clinical data is required to support that the differences in receptor binding, etc., result in a decreased PML risk. See section 7.3.5 for additional information.

7.2.4 Routine Clinical Testing

Section 7.2 provides an overview of routine clinical testing performed as part of the safety assessments and the timing and frequency of laboratory and clinical testing are provided in section 5.3.5.

Reviewer comment: The clinical testing performed as part of routine safety assessments was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Vedolizumab is a humanized monoclonal antibody, and the primary routes of elimination are likely proteolytic degradation and receptor mediated clearance, thus classical in vitro studies (e.g., human liver microsomes/P450 studies) to investigate PK and vedolizumab's interaction potential were not conducted.

No clinical studies were conducted to specifically evaluate the effect of co-administered drugs on the PK of vedolizumab. The potential for vedolizumab to act as a perpetrator of drug-drug interactions is low, as vedolizumab is an antibody and does not modulate cytokines. The potential for vedolizumab to be impacted by other drugs commonly used the UC and CD population (e.g., methotrexate, azathioprine, 6-mercaptopurine, and aminosalicylates) was assessed through population PK modeling from phase 3 studies. Vedolizumab clearance was not affected by co-administration of immunomodulators.

See the Clinical Pharmacology Review for additional details.

Reviewer comment: The metabolic, clearance, and interaction workup performed was adequate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Natalizumab, the only currently approved integrin antagonist, is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis and Crohn's Disease. As a result, integrin antagonists in development have been required to include thorough PML risk identification and

minimization programs in their clinical trials and ensure that premarketing patient drug exposure is sufficient to assess the risk for PML before drug approval. The applicant's approach to evaluating for this potential serious risk is described below.

3326 subjects had received at least 1 dose of vedolizumab in the clinical development program as of the cut-off date for inclusion of safety data in the BLA (14March2013), and there were zero cases of PML. This included 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. One thousand and four (1004) patients received ≥ 24 vedolizumab infusions with 4 weeks follow-up. As described in Section 7.2.1, the applicant's pre-approval safety database size was based on Division recommendations that in order to provide a pre-approval assessment of PML risk in patients with UC and CD that would be adequate to take to Advisory Committee for consideration, a minimum of 900 patients should have received ≥ 24 vedolizumab infusions with 4 weeks post-infusion follow up.

The applicant proposes that based on the safety database provided at the time of submission, they have demonstrated that the risk for PML in UC and CD patients taking vedolizumab is less than the risk for PML in patients taking natalizumab. Although direct comparison of vedolizumab to natalizumab is infeasible, the total number of patients and exposure time of vedolizumab is compared to that of natalizumab when the first three PML cases on it were identified. In clinical trials of natalizumab, two PML cases were identified in 1,869 multiple sclerosis (MS) patients and one PML case in 1,043 Crohn's disease (CD) patients. The overall mean duration of exposure to natalizumab was approximately 18 months. This was based on 3 confirmed cases of PML in 3116 patients exposed for this period of time.

The vedolizumab safety database (as of the June 27, 2013 cutoff date) includes 3,326 patients exposed to at least one dose of vedolizumab. Among these patients, 2,830 (85%) patients filled out at least one subjective checklist as part of the RAMP program. The summary statistics (mean and median) for exposure data is shown in Table 47: Vedolizumab Patient ExposureTable 47, below.

Table 47: Vedolizumab Patient Exposure

		All Patients Exposed to Vedolizumab N =3,326	All Patients Exposed to Vedolizumab w/ RAMP N =2,830
No. of Infusions	Mean (SD)	15.4 (14.2)	17.8 (14.1)
	Median (Min-Max)	9.0 (1.0 – 61.0)	13.0 (1.0 – 61.0)
No. of Infusions with > 28 days FU	Mean (SD)	15.0 (14.0)	17.4 (13.9)
	Median (Min-Max)	9.0 (0.0 – 60.0)	13.0 (0.0 – 60.0)
No. of Months Exposure	Mean (SD)	13.6 (13.4)	15.9 (13.3)
	Median (Min-Max)	7.5 (0.0 – 61.3)	11.6 (0.0 – 61.3)

FU=follow-up; SD=standard deviation; Min=minimum value; Max=maximum value

The summary statistics indicates that the mean duration of exposure of all exposed patients (13.6 months) was shorter than the natalizumab mean exposure time of 18 months with a mean of 15 vedolizumab infusions. When limiting all exposed patients to those who have been assessed under the RAMP (2,830 patients), the mean exposure was 15.9 months with a mean of more than 17 vedolizumab infusions. Therefore, the size of the vedolizumab safety database and duration of patient exposure is roughly similar to the natalizumab safety database when the first three PML cases were observed.

A total of 3326 subjects were exposed to vedolizumab during clinical development with 0 confirmed cases of PML, as of 14March2013 (See section 7.3.5 for specific results). The statistical "Rule of Three" states that, in a study where no events are observed, the 95% confidence upper bound for the true event rate is approximately 3/n, where n is the study sample size (or in this case, the total sample size exposed to vedolizumab) *(Jovanovic, B.D. and Levy, P.S. A Look at the Rule of Three. The American Statistician 1997;51(2):137-139)*. Using this principle, based on 0 cases of PML with 3326 exposed, the upper bound of 95% confidence interval (CI) of the risk estimate for PML in vedolizumab treated patients is 0.90/1000. This risk estimate does not take into consideration duration of treatment and includes exposed subjects who received only 1 dose of vedolizumab.

Longer duration of exposure, especially beyond 2 years, is a known risk factor for PML in patients treated with natalizumab. Table 48 below, provided by the Applicant, compares the PML rates in patients treated with natalizumab with the upper bound 95% CI rate based on zero observed PML events in the vedolizumab safety database, stratified by minimum duration of exposure. The applicant proposes they have demonstrated a lower risk for PML with vedolizumab treatment, when considering duration of exposure.

Table 48: PML Incidence Rates and Risk Estimates

Duration of Exposure	Point Estimate Natalizumab PML Rates[a]	Upper Bound 95% CI Rate for 0 Observed Vedolizumab PML Events (27June 2013 data cutoff)
≥ 12 months	3.15/1000	2.1/1000
≥ 18 months	3.40/1000	2.5/1000
≥ 24 months	3.76/1000	3.3/1000

Source: Modified from Table 3.1 in sponsor Submission: Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab
a Bloomgren et al., 2012

The presence of JC virus antibodies and prior immunosuppressant use are also risk factors known to increase the risk of PML in natalizumab treated patients. These risk factors were included in the risk stratification scheme in Table 49 below, by Bloomgren et al., which includes data on natalizumab patients through February 2012. In this table, the effect of natalizumab exposure on risk of PML is modified by duration of exposure, JC virus antibody positivity, and prior immunosuppressant use. The authors estimated

the risk for PML was lowest among patients negative for anti-JCV antibodies (0.09 per 1000). The risk for PML was highest among patients who were positive for JCV antibodies, had prior immunosuppressant use (within 24 months of therapy), and had received 25 to 48 months of treatment. The PML risk for this group was 11.1 per 1000. *(Bloomgren G, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med 2012; 366(20):1870-80).*

Table 49: Estimated PML Incidence Rates with Natalizumab Stratified by Risk Factor

Natalizumab Exposure[a]	Anti-JCV Antibody Positive[b]	
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1 – 24 months	0.56/1000	1.6/1000
25 – 48 months	4.6/1000	11.1/1000

Source: Table 3-3 of the applicant's document titled, "Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab" (page 5).
[a] Data beyond 4 years of treatment are limited
[b] Risk in anti-JCV antibody positive patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated MS patients are anti-JCV antibody positive.

The applicant's approach is described as follows. First, all 3,326 patients exposed to at least one vedolizumab dose were stratified by the three known natalizumab PML risk factors: longer duration of treatment (beyond 24 months), prior immunosuppressant use, and positive anti-JCV antibody (Table 50). Approximately 80% of vedolizumab patients had prior immunosuppressant use. For anti-JCV antibody status, the applicant used published rates in the literature, and assumed that approximately 50% of patients to be JC virus antibody positive.

Table 50: Vedolizumab Exposure Stratified by Natalizumab PML Risk Factors

Vedolizumab exposure	Anti-JCV Antibody Positive		Anti-JCV Antibody Negative	Total
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use		
1 – 24 months	333	1330	1663	3326
25 – 48 months	84	334	418	835

Source: Table 3-4 of the applicant's document titled, "Progressive Multifocal Leukoencephalopathy Risk Assessment for Vedolizumab" (page 6).

In order to compare the vedolizumab safety database against natalizumab, the applicant applied the risk-stratified PML incidence rates for natalizumab to the vedolizumab exposure stratified by natalizumab PML risk factors. The stratified PML rates in Table 49 were multiplied with the corresponding number of patients in Table 50 and the products were summed up to yield an expected number of PML cases of 6.41 for vedolizumab. Finally, the applicant assumed that PML occurrence among the 3,326 vedolizumab-exposed patients followed a Poisson distribution with a mean of 6.41. Under this assumption, the probability of zero PML cases with the current safety database was very low (~0.1%).

Table 51: Expected PML Cases in Vedolizumab Clinical Development Program, if Risk Similar to Natalizumab (Per the Applicant)

Vedolizumab Exposure	Anti-JCV Antibody Positive	
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1 – 24 months	0.19	2.13
25 – 48 months	0.38	3.71
	Total Expected Cases of PML: 6.41	
	Probability of Observing Zero Cases: 0.017	

The applicant concluded that if the risk of PML among vedolizumab users were similar to natalizumab users, it would be almost certain that a PML case would occur. Because no PML cases were observed in the vedolizumab safety database, the PML risk is, therefore, lower for vedolizumab than for natalizumab.

Reviewer Comment: The applicant does a thorough job of comparing the vedolizumab population with natalizumab treated patients, in order to theoretical projections of vedolizumab risk estimates based on underlying PML risk factors. There are multiple underlying assumptions and limitations to this approach, however.

- *The strategy compares incidence rates of occurrence of PML and risk estimates assuming no PML cases are observed. These are 2 different things.*
- *The natalizumab risk estimates are based almost entirely on MS patients, as >99% of natalizumab use is in this population. It is not known whether the risk for PML in other patient populations receiving natalizumab would be the same. Furthermore, it is not clear to what extent the risk factors for PML in natalizumab treated MS patients may increase the risk in other patient populations receiving alternative treatments.*
- *The more recent data used for these risk estimates includes data from postmarketing spontaneous reporting, so comprehensive data was not available for all patients. For example, JCV antibody testing was only performed on a subset of patients, with available serum samples, in whom PML developed. Assumptions are also made on the overall prevalence of JCV antibody positivity in the background population, based on reported data.*
- *The previously reported false negative rate for JC virus seropositivity was 3%, but more recent data suggests the false negative rate may be even higher. A single measurement of viral activity (JCV antibody testing) is helpful but not sufficient to assess risk.*
- *Less than 15% of natalizumab treated patients have received the drug for more than 4 years, so risk stratification is limited to 48 months. More data is needed to better understand the risk of PML associated with extended duration of treatment.*
- *Prior immunosuppressant use is a recognized risk factor for PML in natalizumab treated patients with MS, however, given the minimal experience with concomitant immunosuppressant use, we still don't really know to what extent*

concomitant immunosuppressant use may increase the risk of PML with natalizumab or vedolizumab.

We can use the "rule of 3" to estimate what level of PML risk has been ruled out, based on the current vedolizumab exposure. This estimates that the risk of PML in vedolizumab treated patients is no more than 2.1/1000, 2.5/1000, 3.3/1000 with exposures of ≥12, 18, and 24 months, respectively. However, comparing these rates with PML rates in natalizumab treated patients should be done with caution. It would be more relevant to determine a benchmark PML incidence rate in vedolizumab treated patients that we believe is acceptable as a comparator.

Historically, PML risk in CDER has been addressed by including PML-explicit language in the product label. Most of these products, however, are used in oncology and transplant patients where there already exists an underlying risk for opportunistic infections and PML. Natalizumab includes PML specific labeling in a Black Box Warning and also has a required REMS with elements to assure safe use (ETASU). The REMS requirement for natalizumab was based on the determination that there was a definitive risk for this serious, and often fatal condition in a population previously not at risk. Given that there have been no cases of PML detected in the vedolizumab clinical development program to date, the risk of PML with vedolizumab remains a theoretical risk. One could thus argue that labeling alone may be an appropriate strategy. On the other hand, an underlying risk for PML has not been seen in patients with UC and CD on other therapies, excluding natalizumab, and the risk for PML has not been entirely ruled out, with the safety database provided by the sponsor. While nonclinical data is reassuring in demonstrating the selectivity of vedolizumab's binding to the α4β7 integrin, the mechanism by which PML develops in patients administered integrin antagonist products is not completely understood and clinical data is needed to estimate risk. It is unclear what evidentiary threshold we may be comfortable with, to rule out level of risk of PML in these patients with a reasonable level of certainty. If this evidentiary threshold has not been met, a rigorous REMS program with ETASU may provide helpful information to the Agency on the risk for PML in these patients, however, it is not clear that it will improve the benefit risk profile for the drug, beyond that which a Black Box Warning and appropriate labeling may provide.

These issues will be discussed at the Advisory Committee on December 9, 2013, and I will provide an addendum to this review, pending the Advisory Committee recommendations.

7.3 Major Safety Results

UC Comparative Safety

In Clinical Trial C13006, the rates of adverse events were similar in the ITT populations, with 84% of patients in the placebo arm having any adverse event, compared to 82% and 81% in the Q8W and Q4W arms, respectively. The results were similar when comparing the combined vedolizumab group and non-intent-to-treat placebo group. More patients in the placebo-ITT arm reported a serious adverse event (16%) than in either of the vedolizumab-ITT arms (Q8W 8%, Q4W 9%). Similarly, a greater proportion of patients discontinued treatment due to adverse events in both placebo arms (placebo-ITT 12%, placebo non-ITT 11%) than in the combined vedolizumab group (6%) or either vedolizumab ITT group (Q8W 6%, Q4W 5%). A summary of adverse events from the C13006 Maintenance Safety Population is provided below.

Table 52: Overall Summary of Adverse Events: C13006 Maintenance Safety Population

Adverse Event Category	Maintenance ITT			Maintenance non-ITT		Combined VDZ
	PLA N = 126	Q8W N = 122	Q4W N = 125	PLA N = 149	Q4W N = 373	VDZ N = 620
Any Adverse event	100 (84)	100 (82)	101 (81)	114 (77)	296 (79)	497 (80)
Drug-related adverse events	40 (32)	37 (30)	37 (30)	38 (26)	126 (34)	200 (32)
Adverse event resulting in discontinuation	15 (12)	7 (6)	6 (5)	16 (11)	23 (6)	36 (6)
Serious adverse event	20 (16)	10 (8)	11 (9)	17 (11)	56 (15)	77 (12)
Serious infection adverse event	4 (3)	3 (2)	2 (2)	4 (3)	7 (2)	12 (2)
Drug-related serious adverse event	4 (3)	3 (2)	1 (<1)	3 (2)	9 (2)	13 (2)
Serious adverse event resulting in discontinuation	7 (6)	2 (2)	0	6 (4)	14 (4)	16 (3)
Deaths	0	0	0	0	1 (<1)	1 (<1)

Source: Clinical Study Report Study C13006, pages 251 - 252

UC and CD Comparative Safety

The proportion of patients with at least 1 adverse event was 84%, 78% and 84% in the ITT placebo, non-ITT placebo, and combined vedolizumab groups, respectively. More patients had AEs believed to be drug related in the combined vedolizumab group (36%) compared to the group which received only placebo (28%, non-ITT placebo). One death (0.3%) occurred during the clinical trial period in the non-ITT placebo group, compared with 5 deaths (0.3%) in the combined vedolizumab group. Adverse events were reported by a higher proportion of patients in CD Trial C13007 (87% combined vedolizumab; 80% non-ITT placebo) compared to UC Trial C13006 (80% combined vedolizumab; 77% non-ITT placebo). Similarly, there were a higher proportion of patients reporting serious AEs in C13007 (24% combined vedolizumab; 16% non-ITT placebo) compared to C13006 (12% combined vedolizumab; 11% non-ITT placebo). Table 53 provides an overall summary of adverse events for the combined UC and CD comparative safety population. *See Dr Gottliebs Crohn's disease clinical review for specific information on CD patients.*

Table 53: Overall Summary of Adverse Events – UC and CD Comparative Safety Population

Adverse Event Category, n (%)	ITT Placebo[a] N = 279	Non-ITT Placebo[b] N = 297	Combined VDZ[c] N = 1434
Any AE	234 (84)	232 (78)	1203 (84)
Any treatment related AE	91 (33)	83 (28)	517 (36)
AE resulting in discontinuation	30 (11)	30 (10)	127 (9)
Serious AE	43 (15)	40 (13)	276 (19)
Serious infection	9 (3)	8 (3)	57 (4)
Drug-related Serious AE	8 (3)	5 (2)	48 (3)
Serious AE resulting in discontinuation	14 (5)	14 (5)	75 (5)
Death	0	1 (<1)	5 (<1)

[a] ITT placebo group includes patients who received vedolizumab during induction and were randomized to placebo during the Maintenance Phase
[b] Non-ITT placebo group includes patients who received placebo during the Induction Phase and continued to receive placebo during the Maintenance Phase. These patients are not included in the combined UC and CD group above
[c] Combined VDZ group includes responders to VDZ induction who were randomized to VDZ treatment (Q4W or Q8W) at Week 6 and patients who received VDZ during the Induction Phase but did not achieve clinical response at Week 6 and continued to receive vedolizumab Q4W during the Maintenance Phase

Long-Term Safety

In considering the long-term safety of vedolizumab, AEs were analyzed across Trial C13008, as well as across qualifying studies for rollover patients. As of June 27, 2013, the overall incidence of AEs was 91% (92% in CD and 89% in UC). The incidence of SAEs was 27% and was also higher among CD patients (31%) than UC patients (20%). Results from a retrospective observational cohort study performed on data from an external administrative database (HealthCore Integrated Research Database [HIRD^{SM}]) were used to provide a benchmark for evaluation of long-term AEs. The database included a broad representation of patients with IBD on a variety of therapies, including biological agents. AE rates per 1000 person years were comparable between C13008 and the HIRD^{SM} database results.

Reviewer comments: The overall rate of adverse events was similar between the treatment groups in the UC and CD comparative safety population, as were the rates of adverse events leading to discontinuation. There were somewhat higher rates of adverse events and serious adverse events reported among CD patients, however, this may be related to the underlying disease process and higher frequency of extraintestinal symptoms and complications of Crohn's disease.

7.3.1 Deaths

There were 13 deaths total across all controlled and uncontrolled studies in UC and CD during participation in clinical studies. All of the deaths occurred during phase 3 studies, 6 during placebo controlled trials and 7 during open-label long term extension trials. One patient with UC receiving vedolizumab died during the Induction Phase of Clinical Trial C13006 (Cohort 2) and 5 CD patients died in Study 13007, 1 from the non-ITT placebo group and the other 4 from vedolizumab groups. Table 54 below

summarizes the number of deaths in patients occurring in the placebo controlled trials, by exposure to vedolizumab.

Table 54: Summary of Deaths from Randomized Controlled Trials

Vedolizumab Exposure	Died	Survived	Total
Exposed[a]	5	1708	1713
Unexposed	1	296	297
Total	6	2004	2010

[a] The exposed population includes patients from the combined vedolizumab group and ITT-placebo group.

Of the 7 patients who died in the open-label extension trial C13008 through June 27, 2013, 3 had UC and 4 CD. The events leading to death among the UC patients were respiratory failure, cerebrovascular accident, and pulmonary embolism, and none were assessed by the investigator to be related to the study drug. Among the CD patients, traumatic intracranial hemorrhage, hepatic neoplasm, suicide, and sepsis led to patient deaths. Only the hepatic neoplasm was assessed as potentially related to the study drug by the study site investigator. Table 55 below summarizes the deaths in the UC population which occurred during participation in clinical studies, and Table 56 summarizes the deaths in the CD population.

Table 55: Narratives of Deaths in UC Patients

Patient ID	Treatment Group	Days after first dose/last dose	Primary cause of death/narrative	Assessment of relatedness by investigator/ FDA reviewer
C13006				
C13006 - 46007-608	Cohort 2 VDZ	14/14	66-year-old male patient from Russia with a history of ischemic heart disease who received a single 300 mg infusion of vedolizumab for induction. The patient died 14 days after infusion due to sudden cardiac death.	Not related/ not related
C13008				
C13006-50016-602	C13006: VDZ induction/ PBO maintenance C13008: VDZ	332/50	49-year-old female from South Africa with a history of Hashimoto's thyroiditis and hypothyroidism who received vedolizumab induction and placebo maintenance in Trial C13006. Pt. received 2 vedolizumab infusions and 7 placebo infusions in C13006 before being discontinued due to lack of efficacy. Patient enrolled in Trial C13008, and after her second vedolizumab infusion she was hospitalized with worsening UC requiring proctocolectomy. Treatments included IV hydrocortisone, and her exacerbation was considered resolved. She was readmitted for a scheduled colectomy. 9 days following surgery she developed an acute abdomen and septic shock and subsequently developed respiratory failure and died.	Not related/ not related
C13006-58023-603	C13006: VDZ induction/ VDZ maintenance C13008: VDZ	195/111	70-year-old female patient from the US with multiple medical conditions including diabetes, hypertension, hyperlipidemia, GERD, and asthma, who received 4 infusions of double-blind vedolizumab in Trial C13006. She was discontinued from the study due to lack of efficacy and enrolled in Trial C13008 for open label vedolizumab. She received 1 dose of open-label vedolizumab and 23 days later experienced a nonserious event of esophageal candidiasis. The patient received no additional doses of vedolizumab following the event, and 13 days later (36 days after last vedolizumab dose) was hospitalized for worsening UC. She underwent a laparoscopic panproctocolectomy, permanent ileostomy, cystopanendoscopy and bilateral ureteral catheterization. Twelve days following surgery she underwent cardiac catheterization with placement of 4 stents for severe myocardial ischemia. She was discharged to rehabilitation and her course was further complicated by pneumonia, nonsustained episodes of ventricular tachycardia, and two cerebrovascular accidents. She died 111 days after her last vedolizumab infusion.	Not related/ not related
C13008-46210-005	VDZ	883/16	72-year-old male patient with a history of coronary heart disease, hypertension, diabetes, and asthma who received 4 doses of vedolizumab 10mg/kg in Trial C13002 and 12 doses of 2mg/kg in Trial C13004 prior to enrolling in C13008. Patient received one 300mg vedolizumab infusion in C13008 and 14 days later was hospitalized with a pulmonary embolism and died.	Not related/ not related

Source: Applicant Submission, Integrated Summary of Safety

Table 56: Narratives of Deaths in CD Patients

Patient ID	Treatment Group	Days after first dose/last dose	Primary cause of death/narrative	Assessment of relatedness by investigator/ FDA reviewer
C13007				
C13007-24001-705	VDZ Q8W	260/45	28-year old male from India who received 8 doses of VDZ in C13007. The patient was hospitalized with an exacerbation of CD and sepsis 22 after his last infusion. A CT showed pneumoperitoneum, however, the investigator managed the patient medically. He developed respiratory failure and was placed on a ventilator. His condition continued to deteriorate, and he died 45 days after his last dose of medication.	Related/ not related
C13007-37005-703	Non-ITT PBO	Placebo/ placebo	75-year old diabetic from New Zealand who received 8 doses of placebo and was hospitalized with CD exacerbation and discontinued from the study. 48-days after his last dose he experienced cardiac arrest and died.	Not related/ not related
C13007-24028-708	VDZ Q4W	98/28	30-year old male from India with a history of pulmonary emboli, DVT, anemia, and malnourishment received 4 doses of VDZ in 13007. Twenty-seven days after his 4th dose he was hospitalized with acute intestinal obstruction and was found to have bronchopneumonia. He subsequently developed cardiac arrest and died.	Related/ not related
C13007-58025-702	VDZ Q4W	97/6	46-year old female from the US with a history of depression, previous suicide attempt, TMJ syndrome, and hypothyroidism who received 5 infusions of VDZ. Six days following her 5th infusion she died from an intentional drug overdose.	Not related/ not related
C13007-58045-730	VDZ Induction	88/75	23-year old male from the US who received 2 doses of VDZ during induction. Seventy-five days after his second dose, the patient's mother was flushing his TPN line when he reported chest pain and shortness of breath. The patient died in transit to the hospital. Autopsy revealed lymphocytic myocarditis and perivascular foreign-body type granulomatous inflammation of the lungs, consistent with IV injection of medications intended for oral administration.	Not related/ not related
C13008				
C13007-07113-703	C13007: PBO induction/ PBO maintenance C13008: VDZ	387/23	63- year old male from Canada who received placebo in C13007 and subsequently enrolled in C13008. Sixteen days after his 14th dose of VDZ in C13008, the patient fell down the stairs, suffered an intracranial hemorrhage, and died. The patient's family reported that he had been drinking before the event.	Not related/ not related
C13007-12013-702	C13007: VDZ induction/ VDZ maintenance C13008: VDZ Q4W	1193/58	51-year old female from the Czech republic who was diagnosed with hepatocellular carcinoma after approximately 3 years of vedolizumab exposure. She had a family history of hepatic carcinoma but was negative for hepatitis B and C. Her LFTs were normal throughout the study, excluding 1 isolated elevation of ALT of 42 U/L about 9 months before presentation. She presented with epigastric pain and was diagnosed following CT and histopathology. She died 2 weeks later.	Related/ Not related
C13007-12017-705	C13007: VDZ induction/PBO maintenance C13008: VDZ	380/98	38-year old male from the Czech republic with a history of depression for which he was receiving fluvoxamine committed suicide 99 days after his 5th infusion of vedolizumab in C13008.	Not related/Not related
C13011-	C13011: PBO	125/125	A 32-year old male from Malaysia who received a single dose	Not related/ not

33003-901	C13008: VDZ		of VDZ in C13008. Approximately 2 months after receiving VDZ he was hospitalized with a CD exacerbation and experienced sepsis. His condition deteriorated and the patient died during the hospitalization.	related

Source: Applicant Submission, Integrated Summary of Safety

After clinical trial completion, there were two additional deaths in UC patients who previously participated in C13006. Specifically:

Patient C13006-28011-602 was a 32 year-old white male patient from Italy who was enrolled in Cohort 2 and received a single infusion of vedolizumab during Induction before withdrawing from the trial. One hundred ten days after his single dose of vedolizumab, he underwent a total colectomy with ileal pouch anastomosis for ulcerative colitis. The patient developed peritonitis requiring a second surgery and subsequently experienced respiratory failure and sepsis. He died from cardiac arrest related to sepsis and multiple organ failure.

Patient C13006-53003-601 was a 32 year-old white male from Switzerland who received blinded vedolizumab during the Induction Phase and achieved clinical response. He was randomized to vedolizumab Q8W during the Maintenance Phase and received 9 additional infusions (5 vedolizumab and 4 placebo) before discontinuing from the trial due to a lack of efficacy. Seventy-one days after his final infusion, biopsies of the descending colon revealed moderately differentiated adenocarcinoma, and the patient underwent total colectomy and subsequent chemotherapy to treat multiple metastases. The patient died 552 days after his final dose of vedolizumab.

FDA Reviewer Comments: When comparing the risk of death in placebo controlled trials, the risk appears to be similar in vedolizumab exposed patients and unexposed patients; however, as previously stated, given the low event rate, any interpretation of these comparisons should be viewed with caution. None of the deaths in UC patients were assessed to be related to study drug, as determined by study investigators and confirmed by the FDA reviewer. In C13007, 2 deaths were assessed as possibly related to study drug by the investigator. Both of these deaths were the result of exacerbation of CD and sepsis/infection. The FDA reviewer believes these CD exacerbations were not likely related to study drug, rather exacerbations due to lack of drug effect in these patients, and therefore would not categorize them as related to study drug. One additional death in a CD patient participating in C13008 was assessed as possibly related to study drug. This was a case of hepatocellular carcinoma occurring approximately 3 years after initiation of vedolizumab. The FDA reviewer believes it is not plausible this death was related to study drug, given the mechanism of action for vedolizumab. Given the low incidence rate, it is difficult to comment further on any potential relationship. Adverse events, including SAEs and deaths, should continue to be collected and assessed in the postmarketing setting.

7.3.2 Nonfatal Serious Adverse Events

UC Comparative Safety

In Trial C13006, maintenance ITT population, there were approximately twice as many patients in the placebo group who experienced at least 1 SAE compared with the vedolizumab treatment groups (16% placebo, 8% Q8W, 9% Q4W). The rates of SAEs were similar between the combined vedolizumab group and the non-ITT placebo group (12% and 11%, respectively). SAEs determined by the investigator to be drug related occurred infrequently and there were no differences seen between treatment arms in the ITT groups (placebo 3%, VDZ Q8W 2%, VDZ Q4W <1%), non-ITT placebo group (2%), or the combined vedolizumab group (2%).

The most frequent non-fatal SAE in the Maintenance Trial ITT group was ulcerative colitis, which occurred in 6% of placebo patients, 2% of Q8W vedolizumab and 3% of Q4W vedolizumab patients. Ulcerative colitis was reported in 64 patients in the Maintenance Phase overall, and the highest rates were reported in the non-ITT groups; 10 placebo patients (7%) and 40 non-ITT vedolizumab patients (11%) reported ulcerative colitis as a serious AE. Infections reported as SAEs were seen in 2-3% of patients, and there were no notable differences between treatment arms. SAEs which were reported by greater than 1 patient by PT are summarized below.

Table 57: Summary of SAEs reported by >1 Patient, by SOC and PT

	Maintenance ITT			Maintenance non-ITT		Combined VDZ
	PLA N = 126	Q8W N = 122	Q4W N = 125	PLA N = 149	Q4W N = 373	VDZ N = 620
Patients with at least 1 SAE	20 (16)	10 (8)	11 (9)	17 (11)	56 (15)	77 (12)
Gastrointestinal Disorders	9 (7)	3 (2)	4 (3)	12 (8)	42 (11)	49 (8)
Colitis ulcerative	7 (6)	3 (2)	4 (3)	10 (7)	40 (11)	47 (8)
Abdominal Pain	0	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Small intestinal Obstruction	0	0	0	1 (<1)	1 (<1)	1 (<1)
Infections and infestations	4 (3)	3 (2)	2 (2)	4 (3)	7 (2)	12 (2)
Wound Infection	0	0	0	0	2 (<1)	2 (<1)
Anal Abscess	0	0	0	0	2 (<1)	2 (<1)
Perirectal abscess	0	0	0	1 (<1)	1 (<1)	1 (<1)
Appendicitis	2 (2)	0	0	0	0	0
Sepsis	0	0	0	1 (<1)	1 (<1)	1 (<1)
Urinary Tract Infection	0	0	0	1 (<1)	1 (<1)	1 (<1)
Respiratory, thoracic, and mediastinal disorders	1 (<1)	0	0	1 (<1)	3 (<1)	3 (<1)
Pulmonary Embolism	0	0	0	1 (<1)	2 (<1)	2 (<1)
Metabolism and nutrition disorders	0	0	0	1 (<1)	2 (<1)	2 (<1)
Dehydration	0	0	0	1 (<1)	2 (<1)	2 (<1)
Investigations	2 (2)	0	0	1 (<1)	1 (<1)	1 (<1)
Hemoglobin decreased	1 (<1)	0	0	1 (<1)	0	0
Neoplasms benign, malignant, and unspecified	2 (2)	1 (<1)	0	0	0	1 (<1)
Colon Cancer	1 (<1)	1 (<1)	0	0	0	1 (<1)
Blood and lymphatic system disorders	1 (<1)	0	0	1 (<1)	0	0
Anemia	1 (<1)	0	0	1 (<1)	0	0

The proportion of patients with serious adverse events in the patients with baseline immunomodulator and/or corticosteroid use was also analyzed in C13006. Patients receiving vedolizumab with baseline concomitant corticosteroids and/or immunomodulators did not have increased rates of serious adverse events, in comparison to patients not on these medications. SAEs which were reported by greater than 1 person are summarized below, based on concomitant immunosuppressant and/or corticosteroid use. No trends were identified.

In addition to the adverse events reported above, a serious case of hepatitis was reported in Study C13006. A 20-year old male patient from Italy who was in the Maintenance non-ITT vedolizumab Q4W group was hospitalized for acute hepatitis 57 days after his fifth and final dose of vedolizumab. Vedolizumab was discontinued, the patient was treated with corticosteroids (dose not provided) and transaminase levels were monitored on a weekly basis with improvement but not normalization over the subsequent month. A liver ultrasound and biopsy showed a pattern compatible with

drug-induced hepatitis and/or chronic autoimmune hepatitis with fibrosis. Prior therapies included azathioprine/6-MP, infliximab, oral 5-ASA, and corticosteroids. Concomitant medications during the trial included oral prednisone (5 mg daily), lansoprazole, calcium, vitamin D3, and multiple herbal products (crataegus laevigata, valeriana, and "Dream" a hawthorn-based homeopathic medicine for insomnia). The event was considered by the investigator to be related to study drug.

Table 58: SAEs by Concomitant Corticosteroid and/or Immunosuppressant Use, by PT

	Placebo, N = 275				VDZ, N = 620			
Preferred Term n (%) Patients Using Concomitant Therapy	No Con N = 74	COR Only N = 106	IMM Only N = 45	COR and IMM N = 50	No Con N = 373	COR Only N = 226	IMM Only N = 114	COR and IMM N = 99
Patients with at least 1 SAE	8 (11)	15 (14)	5 (11)	9 (18)	19 (10)	30 (13)	14 (12)	14 (14)
Colitis ulcerative	3 (4)	10 (9)	1 (2)	2 (6)	13 (7)	15 (7)	10 (9)	9 (9)
Abdominal Pain	0	0	0	1 (2)	0	1 (<1)	0	1 (1)
Small intestinal Obstruction	1 (1)	0	0	0	0	0	1 (<1)	0
Wound Infection	0	0	0	0	0	2 (<1)	0	0
Anal Abscess	0	0	0	0	1 (<1)	0	1 (<1)	0
Perirectal abscess	0	0	0	1 (2)	0	0	1 (<1)	0
Appendicitis	0	1 (<1)	1 (2)	0	0	0	0	0
Sepsis	0	1 (<1)	0	0	0	0	0	1 (1)
Urinary Tract Infection	0	1 (<1)	0	0		0	0	0
Pulmonary Embolism	1 (1)	0	0	0	1 (<1)	1 (<1)	0	0
Dehydration	0	1 (<1)	0	0	2 (1)	0	0	0
Hemoglobin decreased	0	1 (<1)	0	0	1 (<1)	0	0	0
Colon Cancer	1 (1)	0	0	0	0	1 (<1)	0	0
Anemia	0	0	1 (2)	1 (2)	0	0	0	0

No CON = no concomitant immunosuppressant or corticosteroid use, COR only = concomitant corticosteroids only, IMM only = concomitant immunosuppressants only, COR and IMM = concomitant corticosteroids and immunosuppressants
Source: Clinical Study Report Study C13006, Table 14.4.2.6FM

Similarly, when assessing SAEs in the subgroup of patients in C13006 who were prior TNFa antagonist failures, the only SAE that occurred in > 1% of the combined vedolizumab group was ulcerative colitis (8% ITT placebo, 8% non-ITT placebo; 11% combined vedolizumab). No signal of increased frequency of SAEs by PT in the combined vedolizumab group compared to placebo groups was observed.

UC and CD Comparative Safety

The only serious AEs which occurred in ≥ 1% of VDZ/VDZ population were Crohn's disease, ulcerative colitis, and anal abscess. The proportion of patients reporting at least 1 SAE was larger in the VDZ/VDZ group than in the PBO/PBO group. This was largely driven by SAE reporting in C13007. There was a higher overall rate of serious adverse events in Trial C13007 for Crohn's disease, with 199 (24%) of patients in the VDZ/VDZ group reporting at least 1 SAE, compared to 23 (16%) in the PBO/PBO group. The most commonly reported SAEs in C13007 were Crohn's disease and anal abscess which were reported by 99 (12%) and 16 (2%) in the VDZ/VDZ group

compared to 13 (9%) and 1 (<1%) in the non-ITT placebo group. A summary of SAEs occurring in ≥ 1% of the VDZ/VDZ population is provided below.

Table 59: SAEs Occurring in ≥ 1% of the combined vedolizumab population, by SOC and PT

System Organ Class, n (%) Preferred Term	ITT Placebo N = 279	Non-ITT Placebo N = 297	Combined Vedolizumab N = 1434
Patients with at least 1 SAE	43 (15)	40 (13)	276 (19)
Gastrointestinal disorders	27 (10)	30 (10)	180 (13)
Crohn's disease	8 (3)	13 (4)	99 (7)
Ulcerative colitis	7 (3)	10 (3)	47 (3)
Infections and infestations	9 (3)	8 (3)	57 (4)
Anal abscesses	0	1 (<1)	18 (1)

Source: Sponsor Submission, Integrated Summary of Safety
[a] patients received vedolizumab during Induction Phase and were randomized to placebo for the Maintenance Phase
[b] patients received placebo during the Induction Phase and continued to receive placebo during Maintenance Phase
[c] includes the ITT Q8W, ITT Q4W, and the non-ITT vedolizumab Q4W groups.

Results were similar when looking at the subgroup of patients who had previously failed TNFα antagonists. Serious AEs were reported in 15%, 17%, and 21% of patients in the ITT placebo, non-ITT placebo, and combined vedolizumab groups, respectively. Crohn's disease and ulcerative colitis remained the most commonly reported SAEs, with rates similar to those seen in the general study population.

Long-Term Safety

At least 1 SAE was reported for 20% of UC patients and 31% of CD patients when analyzed across Trial C13008, as well as across qualifying studies for rollover patients, as of June 27, 2013. The time adjusted incidence of SAEs per 1000 person-years was also higher for CD than UC patients (186.60 patients/1000 person-years vs. 100.37 patients/1000 person years, respectively). Gastrointestinal disorders were the most commonly reported SAEs, and only Crohn's disease, ulcerative colitis, abdominal pain, and anal abscess were reported by ≥ 1% of total patients. When analyzing SAE rates by duration of vedolizumab exposure, there was no apparent increased frequency seen with longer periods of use, as shown in Table 60 below, which summarizes the most commonly reported SAEs by months of vedolizumab exposure.

Table 60: Summary of SAEs by Months of Exposure

	Months of exposure						
SOC HLT, n(%)	0 to < 3 N = 2830	3 to < 6 N = 2718	6 to <12 N = 2432	12 to <18 N = 1632	18 to <24 N = 1288	24 to <36 N = 1030	36 to <48 N = 551
Patients with at least 1 SAE	251 (9)	211 (8)	242 (10)	126 (8)	63 (5)	93(9)	29 (5)
Gastrointestinal disorders	146 (5)	139 (5)	156 (6)	68 (4)	38 (3)	47 (5)	13 (2)
Gastrointestinal inflammatory disorders NEC	84 (3)	83 (3)	65 (3)	30(2)	21 (2)	12 (1)	2 (<1)
Colitis (excl infective)	29 (1)	29 (1)	43 (2)	17 (1)	8 (<1)	11 (1)	3 (<1)
Gastrointestinal and abdominal pain	9 (<1)	4 (<1)	10 (<1)	7 (<1)	2 (<1)	11 (1)	4 (<1)
Duodenal and small intestinal stenosis and obstruction	9 (<1)	4 (<1)	16 (<1)	10 (<1)	1 (<1)	5 (<1)	0
Infections and infestations	53 (2)	52 (2)	47 (2)	21 (1)	13 (1)	16 (2)	11 (2)
Abdominal and gastrointestinal infections	26 (<1)	20 (<1)	25 (1)	10(<1)	7 (<1)	5 (<1)	7 (1)
Lower respiratory tract and lung infections	7 (<1)	5 (<1)	3 (<1)	0	1 (<1)	4 (<1)	1 (<1)

Source: Applicant Submission, Integrated Summary of Safety, 120-day Safety Update, Table 4-10

Reviewer comments: Serious adverse events were reported in 19% of patients taking vedolizumab compared to 13% of patients who received placebo only. The more commonly reported serious adverse events were largely related to the underlying disease and not likely to be related to drug treatment specifically. In the UC population, these SAEs occurred with similar frequency between treatment arms, though they did occur more commonly in patients treated with vedolizumab among CD patients.

In addition to the above, one case of potential liver toxicity was reported in the 120-day safety data update provided by the Applicant. A 37-year old Polish female patient with a 9-year history of UC completed Study C13006 with no laboratory abnormalities and experienced elevated liver enzymes during the extension Study C13008. Twenty-four days after her 20th dose of vedolizumab Q4W in the C13008 extension study her liver enzymes were moderately elevated. She received one additional dose of vedolizumab 4 weeks later and vedolizumab was then discontinued due to markedly increased liver enzymes (See Table 61 below). Detailed information is not provided on the patient's clinical symptoms, however; it was reported that she did not experience coagulopathy, hepatic encephalopathy, or other evidence of liver failure. She had no history of underlying liver disease, alcohol use, or occupational exposures. Concomitant medications included mesalamine and 6-mercaptopurine. MRI and ultrasound showed an enlarged liver without focal abnormalities, and viral serologies (Hepatitis A, B, C; CMV and EBV) were negative. She had a positive antinuclear antibody test and

subsequently strongly positive results for Anti-Ro52 and antisoluble liver antigen/liver-pancreas antibodies. The patient refused a liver biopsy and was started treatment with methylprednisolone with significant improvement in her transaminase levels.

Table 61: Liver Enzymes: Patient C13006-42016-609

Study Week[a]: Date	ALT (U/L)	AST (U/L)	Total Bilirubin	Alkaline Phosphatase (U/L)
76: 22Feb2013	101 [6, 34]	65 [9, 34]	4 µmol [3, 21]	72 [31, 106]
84: 22Apr2013	1003 [6, 34]	684 [9, 34]	9 µmol [3, 21]	116 [31, 106]
Off-study: 3Jul2013	130 [≤41]	470 [≤32]	3.8 mg/dL [0.2, 1.10]	NR
Maximum Observed (date not provided)	>3000	2192 [≤32]	18.58 mg/dL [0.2, 1.10]	206 [35, 104]

[a] Weeks are counted from first dose of vedolizumab in C13008. Last dose of vedolizumab was at Week 80 (22March2013)
Laboratory normal reference range provided in brackets, when available.

Reviewer Comments: One case of potential drug related liver toxicity was reported in Study C13006 and a second case with the 120-day safety update. Case report information provided for both indicate a possible drug or autoimmune etiology. Both patients were treated with corticosteroids and study drug was discontinued, complicating determination of etiology. Additional information was requested of the applicant, specifically, patient histories for these two patients (including concomitant medications and labwork) from the time of enrollment until the last available follow-up. Continued elevated transaminases may suggest an autoimmune etiology, whereas complete resolution may indicate a probable drug related disorder. In addition, information on any additional cases of hepatitis or liver injury where drug induced or autoimmune hepatitis were considered in the differential was requested. Clinically significant liver injury has occurred with natalizumab use, and this potential adverse event should be included in the labeling and closely monitored in the postmarketing setting with consideration for enhanced pharmacovigilance. An addendum to this review will be provided following response from the applicant to our information request and further internal discussion.

7.3.3 Dropouts and/or Discontinuations

UC Comparative Safety

Patients who discontinued from Trial C13006 for any reason were to return to clinic at the earliest opportunity to complete the Early Termination visit. This visit was identical to the Week 52 assessment and included a physical examination, PML checklist, and appropriate labwork. These patients were also to have completed the Week 66/Final Safety visit and complete a 2-year follow-up survey. Patients with adverse events determined by the investigator as related to study drug were not eligible for Trial C13008, however those with AEs determined to be unrelated were eligible for enrollment in the long-term safety study.

Overall, a high percentage of patients discontinued from Trial C13006, with the highest proportion discontinuing from the non-ITT placebo arm (80%) followed by ITT-placebo arm (62%) and combined vedolizumab arm (52%), respectively. The majority of patients discontinued due to lack of efficacy (48% ITT-placebo, 59% non-ITT placebo, and 38% combined vedolizumab, respectively), and these discontinuations happened primarily during the Maintenance Phase of the Clinical Trial. See Section 6.1.3 Patient Disposition for additional details.

More patients discontinued from Study C13006 for an adverse event from the placebo groups than from the vedolizumab groups. Fifteen (12%) patients in the placebo arm discontinued for an AE, compared to 7 (6%) patients in the VDZ Q8W group and 6 (5%) patients in the VDZ Q4W group. Similarly, 16 patients (11%) discontinued from the non-ITT placebo group for an AE, compared to 36 patients (6%) from the combined VDZ group. The most commonly reported AE leading to discontinuation in any treatment arm was ulcerative colitis which was reported more commonly in the placebo groups (8% ITT placebo, 9% non-ITT placebo) than in the combined vedolizumab group (3%). All other AEs leading to study discontinuation occurred in less than 1% of patients in each treatment group. Adverse events leading to discontinuations in at least 1% of patients are summarized in Table 62. This table includes all patients who discontinued at any time from Week 0.

Table 62: C13006 Adverse Events Leading to Discontinuation in ≥1% of Patients from any Treatment Group

	Maintenance Study ITT			Non-ITT[a]		Combined	
Subject Disposition	Placebo N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA N = 149	VDZ Q4W N = 373	PLA N = 275	VDZ N = 620
Discontinued Study (reason)	78 (62)	45 (37)	41 (33)	119 (80)[b]	238 (64)[c]	197 (72)	324 (52)
Lack of Efficacy	61 (48)	31 (25)	33 (26)	88 (59)	171 (46)	149 (54)	235 (38)
Adverse Event (type)	15 (12)	7 (6)	6 (5)	16 (11)	23 (6)	31 (11)	36 (6)
Ulcerative colitis	10 (8)	5 (4)	3 (2)	14 (9)	10 (3)	24 (9)	18 (3)

[a] the non-ITT groups includes patients who discontinued during the induction phase
[b] non-ITT placebo group includes 14 patients who discontinued from the placebo arm during Induction
[c] non-ITT VDZ group includes 43 patients who discontinued from vedolizumab treatment (Cohort 1 or Cohort 2) during Induction

UC and CD Comparative Safety

The overall proportion of patients with at least 1 AE leading to clinical trial discontinuation was similar between the placebo groups and combined vedolizumab groups. The most common AEs resulting in study discontinuation from the combined group were ulcerative colitis and Crohn's disease. No other adverse events led to discontinuation in at least 1% of patients from the combined safety populations. Adverse events leading to discontinuation in the combined safety population are summarized in Table 63.

Table 63: Adverse Events Leading to Discontinuation in ≥1% of the Combined Safety Population

Adverse Event Category	ITT Placebo[a]	Non-ITT Placebo[b]	Combined Vedolizumab[c]
N	279	297	1434
Patients with at least 1 AE resulting in study discontinuation (%)	30 (11)	30 (10)	127 (9)
Gastrointestinal disorders	22 (8)	26 (9)	78 (5)
Crohn's disease	8 (3)	11 (4)	43 (3)
Ulcerative colitis	10 (4)	14 (5)	18 (1)

[a] patients who received vedolizumab during Induction Phase and were randomized to placebo for the Maintenance Phase
[b] patients who received placebo during Induction Phase and continued to receive placebo during Maintenance Phase
[c] includes the ITT vedolizumab groups and the non-ITT vedolizumab group

Reviewer Comments: As also discussed in Section 6.1.3, Trial C13006 had a high proportion of overall discontinuations, with the majority of patients discontinuing due to lack of efficacy or adverse events classified as underlying disease exacerbation (e.g., UC or CD). The higher rate of discontinuation in the placebo arms for these two reasons is expected, and its potential impact on efficacy results is discussed in Section 6.1.3. The narratives for all ulcerative colitis adverse events leading to study discontinuation were reviewed for Trial C13006, and these AEs were found to be appropriately coded and similarly classified in all treatment arms. Three of these AEs were classified as related to study drug, however, this reviewer believes all were unrelated to study drug and were more likely related to the patients underlying disease process.

7.3.4 Significant Adverse Events

These are discussed in section 7.3.5 Submission-Specific Primary Safety Concerns.

7.3.5 Submission Specific Primary Safety Concerns

Vedolizumab is being proposed for the treatment of patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or tumor necrosis factor-alpha (TNFα) antagonist. Treatment with TNF antagonists has been associated with a variety of serious adverse events including opportunistic infections, reactivation of tuberculosis, malignancies, and hypersensitivity reactions. In addition, neurological adverse events and the potential risk for PML were primary safety concerns in this submission (see also section 7.2.6).

Infection-related Events

MAdCAM-1 binding sites are predominantly in the gastrointestinal tract but are also distributed in the nasopharyngeal and oropharyngeal tissue *(Csencsits KL, et al, Mucosal addressin expression and binding-interactions with naïve lymphocytes vary among the cranial, oral and nasal-associated lymphoid tissues, Eur J Immunol 2002. 32:3029-3039)*. Based on this distribution, an increased rate of upper respiratory tract infections may be expected – this is believed to be related to the known mechanism of action and targets of vedolizumab and not related to immunosuppression. Similarly, given vedolizumab's mechanism of action and inhibition of lymphocyte trafficking to the GI tract, there is a risk of increased GI infections, as well as systemic infections from enteric pathogens such as Listeria, Salmonella, and C. difficile and Campylobacter.

UC Comparative Safety:
In C13006, a higher proportion of patients reported at least 1 infection in the ITT placebo and combined vedolizumab groups (41% and 42%, respectively) than in the non-ITT placebo group (31%). The most commonly reported HLT were upper respiratory tract infections, and this appears to have driven the difference in frequency of infections between groups. Other infection HLTs reported in ≥ 4% of patients in the combined vedolizumab arm were lower respiratory tract and lung infections, influenza viral infections, and abdominal and gastrointestinal infections. A similar proportion of patients reported these events in each of the treatment arms. The proportion of patients with infection was higher in the ITT vedolizumab Q8W dosing regimen (51%) compared to the ITT Q4W regimen (45%) and non-ITT placebo (39%), however no significant differences were noted when comparing specific HLTs.

Infections of specific interest with vedolizumab use include clostridium difficile, candida, and herpes infections. These cases occurred more frequently in vedolizumab treated patients, however, all were considered mild to moderate in intensity, most resolved by the end of the study, and only 1 herpes-related infection resulted in study discontinuation. There were no reports of TB in Study C13006.

Table 64: Summary of Infection AEs Occurring in ≥1% of the Combined Vedolizumab Group

	Maintenance Study ITT			Non-ITT		Combined	
High-Level Term, n(%)	PLA N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA N = 149	VDZ Q4W N = 373	PLA N = 275	VDZ N = 620
Patients with at least 1 AE	52 (41)	62 (51)	56 (45)	46 (31)	145 (39)	98 (36)	263 (42)
Upper respiratory tract infections	32 (25)	35 (29)	35 (28)	23 (15)	85 (23)	55 (20)	155 (25)
Lower respiratory tract and lung infections	11 (9)	8 (7)	9 (7)	7 (5)	14 (4)	18 (7)	31 (5)
Influenza viral infections	3 (2)	8 (7)	2 (2)	3 (2)	20 (5)	6 (2)	30 (5)
Abdominal and gastrointestinal infections	7 (6)	4 (3)	5 (4)	4 (3)	15 (4)	11 (4)	24 (4)
Urinary tract infections	6 (5)	5 (4)	4 (3)	5 (3)	12 (3)	11 (4)	21 (3)
Viral infections NEC	1 (<1)	3 (2)	4 (3)	5 (3)	10 (3)	7 (3)	17 (3)
Herpes viral infections	4 (3)	5 (4)	6 (5)	2 (1)	5 (1)	6 (2)	16 (3)
Bacterial infections NEC	0	5 (4)	1 (<1)	2 (1)	4 (1)	2 (<1)	10 (2)
Infections NEC	2 (2)	0	4 (3)	2 (1)	5 (1)	4 (1)	9 (1)
TInea infections	1 (<1)	2 (2)	4 (3)	1 (<1)	1 (<1)	2 (<1)	7 (1)

Source: Sponsor Submission, Integrated Summary of Safety, Table 4-48, pages 231 - 232

Serious infections occurred infrequently in all treatment groups with 20 patients (2%) reporting serious adverse events in the infections and infestations SOC (3% ITT placebo; 3% non-ITT placebo; 2% combined vedolizumab). The frequency of serious adverse events was similar across dose groups. Of the SAEs reported, only anal and perirectal abscess, appendicitis, wound infection, sepsis, and urinary tract infection were reported by more than one patient. These results are summarized in Table 65 below. One report of sepsis occurred in the non-ITT vedolizumab group. Patient C13006-28011-602 received 1 dose of vedolizumab and withdrew from the study. He underwent a total colectomy 110 days later and later developed sepsis and died due to respiratory failure. This was not believed to be related to study drug.

Table 65: Serious AEs reported by > 1 Patient in the Infection and Infestations SOC

	Maintenance Study ITT			Non-ITT**		Combined	
Preferred Term, n(%)	Placebo N = 126	VDZ Q8W N = 122	VDZ Q4W N = 125	PLA N = 149	VDZ Q4W N = 373	PLA N = 275	VDZ N = 620
Patients with at least 1 SAE	4 (3)	3 (2)	2 (2)	4 (3)	7 (2)	8 (3)	12 (2)
Anal abscess	0	0	0	0	2 (<1)	0	2 (<1)
Perirectal abscess	0	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Appendicitis	2 (2)	0	0	0	0	2 (<1)	0
Wound infection	0	0	0	0	2 (<1)	0	2 (<1)
Sepsis	0	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)

UC and CD Comparative Safety

A larger proportion of patients reported at least 1 infection in the combined vedolizumab group (43%) than the non-ITT placebo group (35%). The most commonly reported HLTs were upper respiratory tract infections (17% non-ITT placebo; 24% combined vedolizumab), and this appears to have driven the difference in frequency of infections between groups. Other infection HLTs occurred with similar frequency across treatment arms. PTs in the infections and infestations SOC reported by ≥ 1% of patients in the combined vedolizumab group are summarized below.

Table 66: Infection AEs that occurred in ≥1% of patients in the combined VDZ group by PT

Preferred Term, n (%)	VDZ/PLA N = 279	PLA/PLA N = 297	VDZ/VDZ N = 1434
Pts with at least 1 AE	116 (42)	103 (35)	622 (43)
Nasopharyngitis	29 (10)	21 (7)	180 (13)
Upper Respiratory Tract Infection	19 (7)	19 (6)	106 (7)
Bronchitis	11 (4)	10 (3)	57 (4)
Influenza	10 (4)	5 (2)	51 (4)
Urinary Tract Infection	10 (4)	8 (3)	49 (3)
Sinusitis	10 (4)	3 (1)	44 (3)
Gastroenteritis	10 (4)	3 (1)	35 (2)
Anal Abscess	3 (1)	4 (1)	30 (2)
Pharyngitis	6 (2)	1 (<1)	24 (2)
Oral Herpes	6 (2)	4 (1)	20 (1)
Gastroenteritis, viral	2 (<1)	3 (1)	15 (1)

Source: Applicant Submission, Integrated Summary of Safety, Tables 18.2.2.2A and 18.2.2.16A

Serious infections occurred more frequently in CD patients in C13007 than in UC patients in C13006. In UC patients, serious infections were reported by 20 patients and at a similar frequency across dose groups (3% ITT placebo; 3% non-ITT placebo; 2% combined vedolizumab). In Study C13007, serious infections were reported in 5 (3%), 4 (3%), and 45 (6%) of patients in the ITT placebo, non-ITT placebo, and combined vedolizumab groups, respectively. Anal abscesses were the most frequently reported serious AE among CD patients, and the frequency was highest in the non-ITT vedolizumab group. In addition, there were 4 sepsis-related serious AEs in Study C13007, and 2 of these patients died.

Systemic infections from enteric pathogens occurred in very small numbers, so comparisons are difficult to make. There were no cases of Listeria or Salmonella in C13006 or C13007; however, there were 6 cases of C. difficile and 2 cases of Campylobacter infections in patients who received vedolizumab, and 0 cases in patients who received placebo only. One case of C. difficile in a patient with CD was an SAE that resolved after 5 days, and one case was nonserious but led to study discontinuation. The remaining 4 cases were considered mild to moderate in severity and resolved. In addition, 1 patient from C13011 who received vedolizumab was diagnosed with Campylobacter infection and 1 with salmonella.

Fifty-one patients reported Herpes viral infections, however, none were serious, all were considered mild to moderate in intensity, and the majority were oral herpes. The rates of herpes infections were similar across treatment groups (3% ITT placebo, 2% non-ITT

placebo, and 3% combined vedolizumab). Three herpes infections led to study discontinuation, 1 case of herpes zoster in an ITT-placebo patient from C13006, and 1 case each of herpes zoster and oral herpes in C13007.

A similar AE profile in the infections and infestations SOC was seen for patients with baseline concomitant use of immunomodulators and/or corticosteroids. As in the overall population, a larger proportion of patients in the VDZ/VDZ group (43%) experienced at least 1 infectious AE, compared to 36% in the non-ITT placebo group. The most commonly reported AEs were similar in the subgroup of patients with baseline concomitant use of immunomodulators and/or corticosteroids and included nasopharyngitis, upper respiratory tract infection, bronchitis, and urinary tract infections.

Long-term Safety

The frequency of infections, including commonly reported infections (URI, gastrointestinal, UTI, influenza), fungal infections, and herpes infections did not increase with continued exposure to vedolizumab to 48 months. In addition to the information summarized above, there were 4 reports of tuberculosis among patients treated with vedolizumab which all occurred in the first 18 months of treatment. Three patients in Study C13008 were diagnosed with pulmonary tuberculosis. All three patients were on concomitant corticosteroids, and two were also receiving concomitant azathioprine. All patients had negative screenings for TB at enrollment, so none of these cases were considered to be reactivation of latent disease, and all three patients live in countries with higher endemic rates of TB relative to the US (Russia, South Korea, and India). All were considered to be primary infections, and no extrapulmonary manifestations were reported. In addition, one CD patient from the Czech Republic who was previously treated with azathioprine, 6-mercaptopurine, and systemic corticosteroids was diagnosed with latent tuberculosis. Two days after his final of 3 doses of vedolizumab, the patient had a nonproductive cough; chest X-ray was negative, but mycobacterium T complex tests confirmed a latent TB infection. Patient was discontinued from the study and started on treatment with isoniazid and was reported in good condition.

Table 67: SAEs in the Infections and Infestations SOC that Occurred in > 2 Patients Overall by Preferred Term and Indication

Preferred Term, n (%)	*Ulcerative Colitis N = 894*	*Crohn's Disease N = 1349*	*Total N = 2243*
Patients with at least 1 serious infection adverse event	42 (5)	113 (8)	155 (7)
Anal abscess	0	27 (2)	27 (1)
Gastroenteritis	3 (<1)	13 (<1)	16 (<1)
Pneumonia	7 (<1)	8 (<1)	15 (<1)
Abdominal abscess	0	10 (<1)	10 (<1)
Clostridium Difficile colitis	6 (<1)	4 (<1)	10 (<1)
Appendicitis	4 (<1)	5 (<1)	9 (<1)
Cellulitis	3 (<1)	3 (<1)	6 (<1)
Diverticulitis	1 (<1)	3 (<1)	4 (<1)
Pelvic abscess	1 (<1)	3 (<1)	4 (<1)
Perirectal abscess	0	4 (<1)	4 (<1)
Clostridial infection	1 (<1)	2 (<1)	3 (<1)
Cytomegalovirus colitis	2 (<1)	1 (<1)	3 (<1)
Gastroenteritis viral	0	3 (<1)	3 (<1)
Pulmonary tuberculosis	1 (<1)	2 (<1)	3 (<1)
Urinary tract infection	1 (<1)	2 (<1)	3 (<1)

Source: Sponsor Submission, C13008 Complete Study Report: 120-day safety update

Other notable serious infection AEs reported by ≤2 patients included salmonella, giardiasis, Klebsiella infection, Listeria meningitis, esophageal candidiasis, viral meningitis (Epstein Barr Virus), and sepsis.

Reviewer comment: A higher proportion of patients in vedolizumab treated groups reported 1 or more infectious AE, than in the placebo groups. This appeared to be largely driven by a higher rate of infections involving the upper respiratory and nasopharyngeal tract, and these AEs were generally nonserious. SAEs of infection occurred infrequently and at a similar frequency in all of the treatment groups. Serious infections occurred more frequently in CD patients than in UC patients, and this appeared to be primarily driven by increased numbers of abscesses in the CD population. The number of infections from enteric pathogens was very small and difficult to compare, though there were more cases in the vedolizumab group than placebo. There was no observed increase in AE rates among the subgroup of patients on concomitant corticosteroids and/or immunomodulators.

Infusion-related Events and Hypersensitivity reactions

Infusion-related events were analyzed as AEs assessed by the investigator to be infusion-related and that occurred within 1 calendar day of an infusion. Patients were to be monitored for infusion-related events during and after infusions and report the development of symptoms consistent with infusion-reactions (e.g., hives, pruritus) to the investigator. Adverse events defined by the investigator as infusion-related reactions were in the SOCs of general disorders and administration site conditions, skin and

subcutaneous tissue disorders, immune system disorders, and respiratory, thoracic, and mediastinal disorders.

UC Comparative Safety

Investigator-defined infusion-related events were uncommon but were seen more frequently in patients treated with vedolizumab than placebo in Study C13006 (5% combined vedolizumab vs <1% non-ITT placebo). Three patients, described below, experienced an infusion-related reaction resulting in discontinuation from the study, and an additional 6 vedolizumab-treated patients experienced reactions resulting in study dose interruption or administration of an incomplete dose.

A 47-year-old female reported right eye pruritis and swelling approximately 1 hour after completion of her first and only vedolizumab infusion. She was treated with loratadine and the event had resolved by 9 hours after completion of the infusion. The patient discontinued from the study due to this reaction.

A 28-year old male developed a pruritic, urticarial rash involving the arms, face, and flank approximately 10 minutes after his 6th dose of vedolizumab was started. Hydrocortisone and promethazine were administered and the event resolved by 1 ½ hours after it started. The patient discontinued from the study due to this event.

A 41-year old male developed flushing, tongue thickening, tinnitus, pruritus, and erythema 26 minutes after initiation of his third dose of vedolizumab. The patient was treated with IV hydrocortisone and the event resolved 5 minutes after it started. The patient discontinued from the study due to this event.

UC and CD Comparative Safety

Across the UC and CD phase 3 induction/maintenance studies, 3% of patients who received only placebo had an AE defined by the investigator as infusion-related, compared to 4% of patients who received at least 1 dose of vedolizumab (3% ITT placebo and 4% combined vedolizumab). Four patients discontinued from C13006 and C13007 due to an infusion-related reaction and an additional 11 vedolizumab-treated patients experienced reactions that resulted in interruption of an infusion.

In addition to the 3 patients described above, 1 patient from C13007 experienced an infusion-related reaction resulting in discontinuation from the study.

A 44-year-old female experienced a serious AE of infusion-related reaction 13 minutes after the start of her second vedolizumab infusion. Symptoms included dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate. The infusion was discontinued and the patient treated with IV hydrocortisone, antihistamine, and oxygen. The event resolved by 3 hours after it started. The patient was discontinued from the study due to the event.

Table 68 below summarizes investigator defined infusion-related events in this population.

Table 68: Summary of AEs Defined by the Investigator as Infusion-Related Reactions by SOC and HLT

System Organ Class, n (%) High-Level Term	ITT Placebo N = 279	Non-ITT Placebo N = 297	Combined Vedolizumab N = 1434
Patients with at least 1 AE	**8 (3)**	**9 (3)**	**61 (4)**
General disorders and administration site conditions	5 (2)	4 (1)	16 (1)
Asthenic conditions	2 (<1)	2 (<1)	5 (<1)
Feelings and sensations NEC	0	0	4 (<1)
Infusion site reactions	2 (<1)	1 (<1)	3 (<1)
Febrile disorders	0	0	3 (<1)
Pain and discomfort NEC	1 (<1)	0	1 (<1)
General signs and symptoms NEC	0	0	1 (<1)
Product physical issues	0	0	1 (<1)
Edema NEC	0	1 (<1)	0
Skin and subcutaneous tissue disorders	0	0	14 (<1)
Pruritus NEC	0	0	6 (<1)
Rashes, eruptions and exanthems NEC	0	0	3 (<1)
Urticarias	0	0	3 (<1)
Dermatitis and eczema	0	0	2 (<1)
Erythemas	0	0	2 (<1)
Dermal and epidermal conditions NEC	0	0	1 (<1)
Purpura and related conditions	0	0	1 (<1)
Immune system disorders	0	0	1 (<1)
Allergic conditions NEC	0	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	1 (<1)	0	3 (<1)
Breathing abnormalities	0	0	1 (<1)
Coughing and associated symptoms	0	0	1 (<1)
Upper respiratory tract signs and symptoms	0	0	1 (<1)
Nasal congestion and inflammations	1 (<1)	0	0

Source: Sponsor Submission, Integrated Summary of Safety, page 335 (Table 4-79)

The applicant did not include reduced blood pressure or associated symptoms (e.g., syncope) in their assessment of infusion reactions. This reviewer found an additional 8 vedolizumab treated patients experienced a decrease in blood pressure and 10 vedolizumab treated patients experienced syncope during Studies C13006 and C13007. All but one episode of hypotension resolved, and no patient discontinued from the study secondary to these AE's, so these AEs are not consistent with infusion-reactions or hypersensitivity reactions.

Of patients participating in Study C13008, 3% of UC patients and 4% of CD patients had an investigator defined infusion-related reaction (this includes reactions occurring across the qualifying study, where applicable).

Reviewer comments: Infusion-related reactions occurred infrequently and at a rate of approximately 4% in patients receiving vedolizumab. There was at least 1 case of

anaphylaxis from C13007 (described above) and several cases of urticaria. The potential for infusion reactions should be included in the labeling.

Malignancies:

A total of 17 patients exposed to vedolizumab across the UC and CD clinical development program were diagnosed with malignancy, which were assessed by the investigator as serious. In addition, there were 4 cases of colonic dysplasia reported. This included 6 reported malignancies out of 1434 patients (0.4%) exposed to vedolizumab during the controlled clinical trials, including one patient with basal cell and squamous cell carcinoma. An additional patient from C13006 who received only placebo was diagnosed with malignancy (0.3% of 297 total placebo patients from C13006 and C13007). The remainder of malignancies in patients exposed to vedolizumab occurred during long-term open-label treatment (C13008). There were no reports of malignancies in the Phase 1b and Phase 2 safety population or in Study C13011. Table 69Table 69 below provides a summary of vedolizumab-treated patients with serious malignancies.

Table 69: Summary of Malignancies[1]

Study/Patient ID	Age/ Gender/ Race	Malignancy (Preferred Term)	Number of VDZ infusions/ Days after last infusion	Assessment of relatedness by investigator/ FDA reviewer
UC Patients				
C13006: C13006-37005-605	73.7/M/W	Colon cancer	2/30	No/No
C13006: C13006-53003-691	32.7/M/ W	Colon cancer	7/71	Yes/No
C13006: C13006-58132-603	40.5/M/W	Transition cell carcinoma	2/314	No/No
C13008: C13006-03003-604	47.4/M/W	Malignant melanoma	2/8	No/No
C13008: C13006-04006-647	44.1/M/W	Colon cancer with metastases to peritoneum	8/69	Yes/No
C13008: C13006-07113-603	50.4/M/W	Renal cancer	29/13	Yes/Possibly
C13008: C13006-58104-609	70.2/M/W	Malignant melanoma	9/13	No/No
C13008: C13006-58141-807	75.3/F/W	Malignant lung neoplasm	4/94	No/No
Crohns disease				
C13007: C13007-07024-706	20.7/F/W	Carcinoid tumor of the appendix	13/20	No/No
C13007: C13007-18005-709	45.2/F/W	Breast cancer	2/1	No/No
C13007: C13007-58115-703	52.1/F/W	Squamous cell carcinoma (skin)	10/	No/No
C13008: C13007-12013-702	51.1/F/W	Malignant hepatic neoplasm	41/25	Yes/Possibly
C13008: C13007-19004-708	42.9/M/W	B-cell lymphoma	21/97	No/No
C13008: C13007-42009-703	49.7/M/W	Squamous cell carcinoma (skin)	37/20	Yes/Possibly
C13008: C13007-07032-806	69.0/F/W	Hepatic neoplasm malignant/ Lung cancer malignant	3/15	No/No
C13008: C13011-07015-901	45.5/F/W	Colon cancer	8/16	Yes/No
C13008: C13011-58012-902	46.8/M/W	Basal cell carcinoma	12/18	Yes/Possibly

Source: Sponsor Submission, Integrated Summary of Safety Page 292 and 120-day Safety Updated Pages 48-49
[1] This summary includes malignancies reported as serious by the investigator

The overall incidence rate for colon cancer was 0.66 per 1000 person-years. This is lower than the incidence rate of 2.07 per 1000 person-years found in patients with moderate to severe IBD in the HIRD database.

Reviewer Comments: The overall number of malignancies was low and no malignancy type predominated. Nonclinical data did not suggest carcinogenic potential with vedolizumab (see nonclinical review). In controlled trials, the proportion of patients with malignancies was similar across treatment groups; however, comparisons are difficult to make given the low number of malignancies and limited long-term exposure. The rates of colon cancer appear to be consistent with what is expected in this patient population, based on the HIRD database.

Neurologic-related Events

UC Comparative Safety

A similar proportion of patients reported at least 1 nervous system event in each treatment arm with 28 (19%) of placebo patients and 129 (21%) of combined vedolizumab treated patients reporting at least one neurological AE. The rates were similar in the patients who received vedolizumab during induction and placebo during the maintenance phase (18% placebo-ITT). The most frequently reported HLT was Headaches NEC which was reported at similar rates in the combined vedolizumab and ITT-placebo group and less frequently in the non-ITT placebo group (13% ITT placebo; 10% non-ITT placebo, 14% combined vedolizumab). The next most common HLT reported was Neurological signs and symptoms NEC, which was reported at similar rates across groups (2% ITT placebo; 1% non-ITT placebo, 4% combined vedolizumab). No patient discontinued from Study C13006 due to a nervous system event, and only one event was designated as serious by the investigator (syncope by patient in ITT VDZ Q4W group).

UC and CD Comparative Safety

The results were similar in the Phase 3 Crohn's Disease Studies. In Study C13007, 30% of patients in the ITT-placebo arm reported at least 1 nervous system event, compared to 20% and 22% in the non-ITT placebo and combination vedolizumab arms, respectively. Of note, paresthesias and dysesthesias were approximately equally distributed between the vedolizumab and placebo arms in C13006 (1.2 % and 1.3 %, respectively). In Study C13007, however, paresthesias and dysesthesias were observed in 2.79 % of 718 vedolizumab treated patients in study C13007 and there were no reports in 148 placebo treated patients.

Long-term UC and CD Safety

In the long-term safety study, C13008, 30% of patients reported at least 1 nervous system AE as of June 27, 2013, with headaches reported most commonly in UC and CD patients. Nervous system AEs were reported with similar frequencies for UC and

CD patients. Nervous system AEs reported by greater than 1% of patients are summarized by indication in Table 70, below.

Table 70: Nervous System AEs in Long-term Safety Group

High Level Term, n (%)	Ulcerative Colitis N = 894	Crohn's Disease N = 1349	Total N = 2243[a]
Patients with at least 1 nervous system AE	242 (27)	437 (32)	679 (30)
Headaches NEC	141 (16)	266 (20)	411 (18)
Neurological signs and symptoms NEC	41 (5)	101(7)	147 (7)
Sensory abnormalities NEC	32 (4)	51 (4)	85 (4)
Paresthesias and dysesthesias	21 (2)	31 (2)	73 (3)
Migraine headaches	19 (2)	27 (2)	51 (2)

Source: Sponsor Submission, Integrated Summary of Safety, 120-day Safety Update, Table 4-21
[a] For patients in C13008 who received vedolizumab in qualifying studies and rolled into C13008, the frequency of AEs was analyzed across the originating study and Study C13008. For patients who received placebo during the previous study, AEs were not counted during the time of placebo administration.

Reviewer comment: Neurologic AEs were generally reported at similar rates with vedolizumab (21% C13006; 22% C13007) and placebo (19% C13006; 20% C13007) in Phase 3 controlled trials. The exception was paresthesias and dysesthesias which were reported at a higher frequency in vedolizumab treated patients than placebo treated patients in Study C13007. This difference was not seen in C13006 (paresthesias and dysesthesias were reported in 2-3% of patients with long-term treatment). The lack of such a reporting difference in UC patients during controlled trials is difficult to explain, and it is possible the difference in CD patients is related to underlying disease or chance. Continued monitoring for drug-induced neuropathies in the postmarketing setting may be warranted. The most frequently reported neurologic AEs were headache and dizziness.

PML Assessment: RAMP Algorithm

No cases of PML have been identified in the completed trials and ongoing long-term extension Study C13008, as of the 120-day safety cut off date of June 28, 2013. In the ongoing and completed trials which utilized the RAMP algorithm, a total of 290 (10%) patients have reported at least one abnormality on the subjective PML checklist. Of the 290 patients, all were administered the objective PML checklist, and 64 had abnormal findings identified. The positive objective findings varied and included abnormal sensory exam, difficulties with 2-point discrimination in extremities, decreased pinprick sensation, sensory neuropathy, problems with recall and memory, and muscle weakness. Fifty-eight MRIs were performed and 86 cases have been adjudicated by the IAC. Five lumbar punctures have been performed, and these cases are described below. No cases of PML have been detected thus far in 2927 patients monitored through the RAMP program.

Table 71: Summary of RAMP Algorithm Results from Phase 2 and 3 Studies[a]

PML Checklist	Ulcerative Colitis	Crohn's Disease	Total
Number of patients, n (%)	**1146**	**1781**	**2927**
Subjective checklist administered[b]	1142 (> 99)	1771 (> 99)	2913 (> 99)
Positive subjective findings	97 (8)	193 (11)	290 (10)
Objective checklist administered	97 (8)	193 (11)	290 (10)
Abnormal finding on objective checklist	17 (1)	47 (3)	64 (2)
Summary of RAMP algorithm, n (%)			
Referred to a neurologist	24 (2)	61 (3)	85 (3)
MRI performed	15 (1)	43 (2)	58 (2)
IAC involved	24 (2)	62 (3)	86 (3)
Lumbar puncture	2 (<1)	3 (<1)	5 (<1)
CSF analysis for JCV by PCR	2 (<1)	3 (<1)	5 (<1)
JCV DNA detected by PCR in CSF	0	0	0
Diagnosed with PML by the IAC	0	0	**0**

Source: Applicant Integrated Summary of Safety and 120-day Safety Update (Table 6-1)
[a] includes Studies C13002, C13004, C13006, C13007, C13008, and C13011
[b] proportions are based on number of patients completing at least 1 subjective checklist

Five patients had LPs performed as part of the evaluation of symptoms (1 patient in C13006, 2 patients in C13007, 2 patients in C13008). There was no JCV DNA detected in any of the CSF samples, and no patients were diagnosed with PML by the IAC. Brief narratives for the 5 patients who had LPs performed are provided below.

Patient C13006-58098-607 is a 44-year old white female from the US enrolled in Study C13006 who was in the maintenance non-ITT vedolizumab group and was receiving vedolizumab 300 mg Q4W. Eight days after the patient received her 5th dose of vedolizumab (Week 14 visit), she experienced persistent memory problems which the investigator considered nonserious and unrelated to the study drug. At the Week 18 and Week 26 visits, the patient's subjective checklists were positive for problems with memory/thinking and difficulty reading/blurry vision, respectively; however, the patient had normal objective checklists at these visits. At Week 30 (16 days after the patient's 8th and final dose of vedolizumab), she experienced joint/muscle fatigue and weakness and had abnormal objective test results. An MRI had findings that could possibly represent a very early form of PML and a lumbar puncture was performed 12 days later. Results were normal, and the IAC determined that the clinical presentation and findings were not consistent with PML and that the MRI showed no evidence of the disease. Follow-up MRI 3 weeks after the original study showed no significant change. The patient had no changes at her final study follow-up visit, which occurred approximately 2 months after PML was excluded by the IAC.

Patient C13007-19002-705 is a 39-year old white female from Germany enrolled in Study C13007 who was in the maintenance ITT Q4W vedolizumab group. She reported eye floaters and impaired vision on her Subjective Checklist administered 27 days after her 8th dose of vedolizumab. Neurological examination was normal, MRI was unremarkable, and CSF was within normal limits. An EEG was also performed and was unremarkable. An ophthalmology consultation was completed and no cause for the intermittent visual disturbance could be identified. The IAC believed the case was

inconsistent with PML and may represent a migraine variant. Her symptoms resolved and the patient completed Study C13007 and entered Study C13008.

Patient C13007-18008-704 is a 54-year-old white male from France who was enrolled in Cohort 2 of Study C13007 and reported numbness in both legs on his Subjective Checklist 30 days after his 12th dose of vedolizumab. Objective testing confirmed a sensory neuropathy and EMG revealed sensory polyneuropathy of the lower limb. MRI showed no evidence of ischemic stroke, hemorrhage sequelae, displacement of midline structures, edema, or masses. LP was negative for JCV DNA. The case was reviewed by the IAC and PML was excluded. The patient completed study C13007 and entered C13008.

Patient C13006-58140-601 is a 37-year-old white male from the US with UC who received placebo in Study C13006 and discontinued after Week 6 due to lack of efficacy. The patient enrolled in Study C13008 and received 1 dose of vedolizumab. Seven days after he received treatment he was hospitalized with bloody diarrhea with myalgias, arthralgias, lower extremity weakness, fever, and nonproductive cough. Stool specimen was positive for C. difficile, and he was started on metronidazole. An MRI showed a nonspecific and poorly defined region of hyperintense signal abnormality within the right frontal lobe. LP was negative for JCV DNA. The case was reviewed by the IAC and PML was excluded.

Patient C13011-58025-903 is a 27-year-old white male from the US with CD who received placebo in Study C13011 and enrolled in Study C13008. One day following his first infusion he reported paresthesias, numbness, and tingling in hands and toes, as well as fatigue and memory difficulties. MRI was negative and LP was negative for JCV DNA. Nerve conduction studies showed compression of the right ulnar nerve. The IAC reviewed the case and concluded it was inconsistent with PML. The paresthesia was ongoing at last report and considered by the investigator to be related to study drug.

UC and CD Comparative Safety Population:
Positive subjective findings were reported at similar rates in the combined vedolizumab, and ITT-placebo, and non-ITT placebo treatment groups in Studies C13006 and C13007 (7%; 6%, and 8%, respectively). Similarly, no difference was noted in the rates of abnormal objective findings between groups (2% ITT placebo; 1% non-ITT placebo, 1% combined vedolizumab). The findings were similar between studies. A summary of the RAMP algorithm results from Studies C13006 and C13007 is provided below.

Table 72: Summary of RAMP Algorithm Results from Phase 3 Induction/Maintenance Safety Population (C13006 and C13007)

	C13006			C13007			Combined		
PML Checklist	**ITT PLA**	**Non-ITT PLA**	**VDZ**	**ITT PLA**	**Non-ITT PLA**	**VDZ**	**ITT PLA**	**Non-ITT PLA**	**VI**
Number of patients, n (%)	**126**	**149**	**620**	**153**	**148**	**814**	**279**	**297**	**14**
Subjective checklist administered[b]	126 (100)	147 (>99)	618 (>99)	153 (100)	148 (100)	807 (>99)	279	295 (>99)	14 (>9
Positive subjective findings	6 (5)	12 (8)	37 (6)	13 (8)	5 (3)	72 (9)	19 (7)	17 (6)	109
Objective checklist administered	6 (5)	12 (8)	37 (6)	13 (8)	5 (3)	72 (9)	19 (7)	17 (6)	109
Abnormal finding on objective checklist	0	4 (3)	4 (<1)	5 (3)	0	12 (1)	5 (2)	4 (1)	16
RAMP algorithm, n (%)									
Referred to a neurologist	0	4 (3)	7 (1)	5 (3)	1 (<1)	18 (2)	5 (2)	5 (2)	25
MRI performed	0	2 (1)	4 (<1)	3 (2)	1 (<1)	12 (1)	3 (1)	3 (1)	16
IAC involved	0	3 (2)	6 (<1)	5 (3)	1 (<1)	17 (2)	5 (2)	4 (1)	23
Lumbar puncture	0	0	1 (<1)	0	0	2 (<1)	0	0	3 (
CSF analysis for JCV by PCR	0	0	1 (<1)	0	0	2 (<1)	0	0	3 (
JCV DNA detected by PCR in CSF	0	0	0	0	0	0	0	0	0
Diagnosed with PML by the IAC	0	0	0	0	0	0	0	0	0

Reviewer comments: The RAMP program was thorough, and no cases of PML were identified through the 120 day safety data cutoff. This included 903 patients exposed to 24 or more vedolizumab infusions with 4-weeks of follow up.

Assessment of JC Viremia:

Real time testing and monitoring for serum JCV DNA was not required during the vedolizumab clinical development program; however, the sponsor was required to batch test for JCV viremia at specific time points, according to the schedule specified in the individual trials. Patients with persistent or increasing viremia were to be reviewed by the IAC. Few patients tested positive for JCV DNA during Phase 3 Studies. Three patients in Study C13006 and 5 patients in Study C13007 tested positive for serum JCV DNA at any point during the study. Only 1 patient (from Study C13007) had a positive JCV DNA test and also had a positive RAMP algorithm result. The positive JCV DNA test occurred at the Screening visit and the positive RAMP algorithm occurred during Study C13008. Review by the IAC concluded that the case was not consistent with PML, and the patient was diagnosed with relapsing remitting multiple sclerosis following MRI and neurology consultation. The patient continued to receive study drug in Study C13008 and subsequent Subjective Checklists were negative.

Table 73: Summary of JC Viremia During Phase 3 Trials

	C13006		C13007		C13011		C13008[a]	TOTAL	
	PLA[c] N = 275	VDZ[d] N = 620	PLA[c] N= 301	VDZ[d] N = 814	PLA N = 207	VDZ N = 209	VDZ N = 1822	PLA[c] N = 783	VDZ[d] N = 3465
Subjects tested	271	605	300	791	203	201	1731	774	3328
Transiently positive, n(%)	1 (<1)	2 (<1)	1 (<1)	4 (<1)	0	0	8 (<1)	2 (<1)	14 (<1)
Persistently positive[b], n (%)	0	0	0	3 (<1)	0	0	1 (<1)	0	4 (<1)
Negative, n (%)	271 (100)	605 (100)	300 (100)	788 (>99)	203 (100)	201 (100)	1730 (>99)	774 (100)	3324 (>99)
Specimens tested	1166	3004	1351	3541	204	202	10929	2721	17676
Positive, n (%)	1 (<1)	2 (<1)	1 (<1)	9 (<1)	0	0	9 (<1)	2 (<1)	20 (<1)
Negative, n (%)	1165 (>99)	3002 (>99)	1350 (>99)	3532 (>99)	204 (100)	202 (100)	10920 (>99)	2719 (>99)	17656 (>99)

[a] JC Virus testing was discontinued with C13008 Amendment #8 and with agreement of the Agency per Type C meeting on September 6, 2011.
[b] persistently positive is defined as detectable viremia on 2 separate occasions over a 180-day period and separated in time by at least 30 days
[c] PLA group includes patients from the non-ITT placebo group who received only placebo, as well as patients from the ITT-placebo group, who received 2 doses of vedolizumab during Induction and were randomized to placebo for the maintenance phase
[d] VDZ group includes patients who received vedolizumab throughout the entire clinical trial

Reviewer Comment: Less than 1% of patients tested positive for JC viremia, and JCV antibody testing was not included in the RAMP program. Positive JCV Antibody status is known to increase the risk for PML in MS patients taking natalizumab and is believed to be a general risk factor for PML infection. Approximately 50% of the general population is believed to be JCV Ab positive, indicating a past infection with JCV. The clinical relevance of JCV viremia as a risk stratification marker is less well defined, though its presence in the CSF is an important diagnostic marker for disease. The vedolizumab clinical development program included batch testing for JC viremia with the implementation of the RAMP algorithm, and the rate of positivity was quite low among those tested. No relationship was found between JC viremia and positive neurological symptoms, and no patients developed PML. However, the small number of patients with positive JCV DNA and the lack of PML cases in the dataset precludes any definitive conclusions regarding the impact of JCV viremia on PML risk.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse events in C13006 and C13007 were nasopharyngitis, headache, arthralgia, Crohn's disease, pyrexia, abdominal pain, upper respiratory tract infection, and ulcerative colitis. The rates of common adverse events were similar between the combined vedolizumab group and the non-ITT placebo group.

The frequency of AEs occurring in at least 5% of patients in the combined vedolizumab group are summarized in Table 74 below.

Table 74: Common AEs in CD and UC - Induction and Maintenance (Studies C13006 and C13007)

	ITT Placebo	Non-ITT Placebo	Combined Vedolizumab
Preferred Term, n (%)	**Patients n (%) N = 279**	**Patients n (%) N = 297**	**Patients n (%) N = 1434**
Patients with at least 1 AE/Total Number of events	234 (84)	232 (78)	1203 (84)
Nasopharyngitis	29 (10)	21 (7)	180 (13)
Headache	43 (15)	32 (11)	177 (12)
Arthralgia	36 (13)	29 (10)	166 (12)
Crohn's Disease	29 (10)	36 (12)	164 (11)
Nausea	26 (9)	23 (8)	128 (9)
Pyrexia	30 (11)	22 (7)	127 (9)
Abdominal Pain	20 (7)	29 (10)	114 (8)
Upper respiratory tract infection	19 (7)	19 (6)	106 (7)
Colitis ulcerative	29 (10)	29 (10)	97 (7)
Fatigue	14 (5)	10 (3)	86 (6)
Vomiting	14 (5)	16 (5)	75 (5)
Anemia	10 (4)	20 (7)	70 (5)
Cough	10 (4)	10 (3)	70 (5)

Source: Sponsor Submission Integrated Summary of Safety, pages 167-168

The frequency of AEs considered severe was also similar across the 3 treatment groups in Studies C13006 and C13007. Thirteen percent of patients in the PBO/PBO group reported severe AEs, compared to 14% in the VDZ/PBO group and 15% in the VDZ/VDZ group. Crohn's disease, abdominal pain, and ulcerative colitis were the only AEs categorized as severe which were reported in at least 1% of the combined vedolizumab group, and these occurred at similar frequencies in the 3 treatment groups.

Reviewer comment: In both the UC and CD populations, infections involving the upper respiratory tract and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection) were the most commonly reported infection and occurred with greater frequency in vedolizumab treated patients than placebo. Oronasal-associated lymphocytes show primary α4β7 expression, suggesting the MAdCAM-1 interactions have a role in nasal infections. The greater frequency of upper respiratory tract infections is consistent with vedolizumab's mechanism of action in inhibiting the α4β7-MAdCAM-1 interaction, and there was no increase in serious infection related adverse events seen. There is the potential that this represents an off target event, however, and this should continue to be monitored in the post-marketing setting. Furthermore, including language that vedolizumab is (b) (4) *may be misleading and this reviewer believes should be omitted.*

7.4.2 Laboratory Findings

Combined UC and CD Population:

In both the UC and CD Induction and Maintenance Safety Populations, there were no clinically important treatment group differences in the proportion of patients who had shifts from baseline to on-study laboratory values. The most common marked laboratory abnormality in Studies C13006 and C13007 was absolute lymphocyte counts < 0.5 x 10^9/L, which was observed in approximately 5% of patients who received vedolizumab. This lab abnormality was also observed in 6% of patients who received placebo only. No patients in Studies C13006 or C13007 met the laboratory criteria for Hy's law laboratory criteria for drug-induced liver injury (ALT ≥3 x ULN and bilirubin ≥ 2 x ULN at the same visit).

Table 75: Summary of Marked Abnormalities[1] in Clinical Lab Values for the Combined Safety Population (C13006 and C13007)

Analyte, n (%)	ITT Placebo N = 279	Non-ITT Placebo N = 297	Combined Vedolizumab N = 1434
Hemoglobin ≤ 70 g/L	1 (<1)	3 (<1)	20 (1)
Lymphocytes < 0.5 x 10^9/L (absolute count)	10 (4)	18 (6)	70 (5)
Leukocytes < 2.0 x 10^9/L (absolute value)	1 (<1)	2 (<1)	4 (<1)
Platelets <75.0 x 10^9/L	2 (<1)	1 (<1)	0
Neutrophils < 1.0 x 10^9/L (absolute count)	4 (1)	3 (1)	6 (<1)
Prothrombin time > 1.25 x ULN	10 (4)	12 (4)	59 (4)
ALT > 3.0 x ULN	6 (2)	3 (1)	22 (2)
AST > 3.0 x ULN	7 (3)	0	16 (1)
Bilirubin > 2.0 x ULN	2 (<1)	2 (<1)	7 (<1)
Amylase > 2.0 x ULN	3 (1)	8 (3)	20 (1)
Lipase > 2.0 x ULN	3 (1)	8 (3)	28 (2)

Source: Sponsor Submission, Integrated Summary of Safety, Table 18.2.3.1
[1] Marked abnormalities were outside the pre-defined criteria for marked abnormality and had an on-treatment value more extreme than the baseline value

Reviewer Comments: Changes in laboratory findings were infrequent and similar between treatment groups.

Long-term UC and CD Safety
One case of potential liver toxicity was reported in the 120-day safety data update provided by the Applicant. The patient was treated with methylprednisolone and is improving. Please see Section 7.3.2 for detailed information.

7.4.3 Vital Signs

No clinically important treatment differences in the mean change in vital signs were observed between-groups in the UC and CD Induction/Maintenance Safety Population.

7.4.4 Electrocardiograms (ECGs)

In Study C13006, 2 patients from the non-ITT placebo group and 3 patients from the combined vedolizumab group had clinically significant ECG abnormalities over the course of the study. The ECG abnormalities included sinus tachycardia with PVCs, sinus rhythm with PACs, LVH secondary to hypertension, ventricular ectopic beat, and atrial fibrillation. No patients discontinued prematurely from Study C13006 due to ECG abnormalities. An additional 5 patients had clinically significant ECG findings during the long-term safety study, C13008. Two UC patients and 3 CD patients had abnormal ECG findings, four of which were assessed by the study investigator as not related to study drug. One ECG finding of coronary sinus rhythm, incomplete right bundle branch block in a 20-year-old patient with CD was reported as mild and related to vedolizumab. A repeat ECG 1 month later was within normal limits.

Reviewer Comments: There does not appear to be an increase in ECG abnormalities in vedolizumab treated patients.

7.4.5 Special Safety Studies/Clinical Trials

Study C13012 was a phase 1 single-arm study in healthy adults to assess the effects of a single 450mg intravenous dose of vedolizumab on the CD4+:CD8+ lymphocyte ratio in the CSF of humans. One hypothesis on the etiology for the increased risk of PML with natalizumab is that it prevents the ingress of leukocytes into the CNS. Vedolizumab did not affect CD4+ counts, CD8+ counts, or the CD4+:CD8+ lymphocyte ratio in the CSF of the subjects studied. The applicant suggests that this supports that vedolizumab is unlikely to lead to impairment of the CNS immune system and potentially increased PML risk.

No special safety studies were performed in the vedolizumab clinical development program. The RAMP algorithm was developed to mitigate the risk of PML and identify early any potential PML cases. This is described in detail in sections 7.2.6 and 7.3.5.

7.4.6 Immunogenicity

See the Clinical Pharmacology Review, Lanyan Fang, PhD, for additional information on immunogenicity.

The immunogenicity of vedolizumab was assessed across multiple studies and the effects of human antihuman antibodies (HAHA) on safety were evaluated. A validated ELISA immunoassay with a sensitivity of 440 pg/mL was used to determine the presence of HAHA. Immunogenicity assessment consisted of an initial screening using dilutions of 1:5 and 1:50; positive samples were subsequently confirmed positive, titered, and tested for neutralization. Patients were considered to be transiently positive

if they had at least one positive HAHA sample and no consecutive HAHA positive samples, while patients categorized as persistently positive had 2 or more consecutive positive samples. To better characterize the overall immunogenicity rate in vedolizumab exposed patients, immunogenicity assessments were performed at 5 half-lives (16 weeks) after the final dose.

In Studies C13006 and C13007, patients were tested for HAHA and neutralizing HAHA against vedolizumab at Weeks 0 (predose), 6, 14, 26, 38, 52 (or Early Termination), and 66 (Safety Visit).

UC Comparative Safety:
In Study C13006, 48 patients (6%) treated with vedolizumab at any point had a positive HAHA blood test, of whom 24 were persistently positive and 28 had neutralizing antibodies. Of patients receiving continuous vedolizumab, 23/620 (4%) had a positive HAHA blood test and 1% were persistent. An additional 5 patients receiving placebo only had positive HAHA samples. There was an apparent higher rate of HAHA in patients who received only 2 doses of vedolizumab than in those receiving drug throughout the 52-week study; 25 (20%) of patients in the ITT placebo group had a HAHA-positive sample at any time, and 18 of these were persistent. The frequency of positive HAHA, both transient and persistent, was lower in patients receiving baseline concomitant immunosuppressant therapy. Of the 48 HAHA-positive vedolizumab treated patients, 8% had infusion related reactions (17%, if looking at the persistently positive subset). PK data showed very low vedolizumab trough concentrations in patients that were persistently HAHA positive. While the number of these patients was small, none of the patients with persistently positive HAHA achieved clinical remission during the induction or maintenance phase, indicating that persistently positive HAHA could have an impact on drug efficacy. This must be considered in light of the low numbers of patients, however.

UC and CD Comparative Safety:
In the group of patients who received continuous vedolizumab in the induction and maintenance phases of C13006 and C13007, 56 of 1434 (4%) were HAHA-positive at any time. Of these patients, 9 were persistently positive, and 33 developed neutralizing antibodies. The overall rate of HAHA-positive off drug (defined as 5 half-lives or 16 weeks after last dose) was 10% (32 out of 320 patients). Co-administration with immunosuppressants appeared to decrease the overall HAHA rate and the rate of persistent HAHA and neutralizing antibodies. This was particularly evident in the ITT-placebo group (n = 279) where only 1 (3%) patient who received concomitant immunomodulator therapy was HAHA-positive, compared to 30 (12%) patients who did not receive concomitant therapy.

Three of 61 (5%) combined vedolizumab patients who had an infusion-related reaction were persistently HAHA positive, while 6 of 1320 (<1%) who did not have an infusion reaction were persistently positive. See Table 76 below.

Table 76: Summary of AE Defined by Investigator as Infusion-Related Reactions by HAHA status

AEs Defined by Investigator as Infusion-Related Reactions (Yes/No)	ITT			Non-ITT		Combined
	Placebo N = 279	VDZ Q8W N = 276	VDZ Q4W N = 279	Placebo N = 297	VDZ Q4W N = 879	VDZ N = 1434
Yes, n (%)						
HAHA-negative	7 (88)	11 (92)	18 (100)	9 (100)	29 (94)	58 (95)
HAHA-positive	1 (13)	1 (8)	0	0	2 (6)	3 (5)
Transiently positive	0	0	0	0	0	0
Persistently positive	1 (13)	1 (8)	0	0	2 (6)	3 (5)
Any Neutralizing HAHA-positive	0	0	0	0	2 (6)	2 (3)
No, n (%)						
HAHA-negative	227 (84)	257 (97)	258 (99)	279 (97)	805 (95)	1320 (96)
HAHA-positive	44 (16)	7 (3)	3 (1)	8 (3)	43 (5)	53 (4)
Transiently positive	14 (5)	6 (2)	3 (1)	3 (1)	38 (4)	47 (3)
Persistently positive	30 (11)	1 (<1)	0	5 (2)	5 (<1)	6 (<1)
Any Neutralizing HAHA-positive	24 (9)	4 (2)	3 (1)	4 (1)	24 (3)	31 (2)

Source: Sponsor Submission, Summary of Clinical Pharmacology 2.7.2, Table 6-3
Transiently positive: all patients who have at least one positive HAHA sample and no consecutive HAHA-positive samples
Persistently positive: all patients who have 2 or more consecutive positive HAHA samples

Reviewer comments: The presence of HAHA may slightly increase the risk of infusion reactions; however, the small number of HAHA positive patients as well as the small number of infusion reactions precludes any definitive conclusions. There are limitations in the assessment of immunogenicity. For example, the observed incidence of HAHA may be an underestimation due to drug interference in the assay and can also be influenced by sample handling, timing of sample collection, concomitant medications, and underlying disease.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See individual adverse event sections described elsewhere. No dose dependent AEs were noted.

7.5.2 Time Dependency for Adverse Events

When looking at AE rates by duration of vedolizumab exposure in Study C13008, no increased frequency of AEs were seen with longer periods of use, nor were any time dependent AEs identified. See Table 60 for a summary of serious adverse events by months of drug exposure.

7.5.3 Drug-Demographic Interactions

The applicant analyzed the safety datasets by age, race, sex, body weight, baseline disease activity, and creatinine clearance in the UC and CD combined safety populations.

There were insufficient numbers of patients ≥ 65 years of age (< 3% of the UC and CD Maintenance Safety Population) to allow meaningful comparisons between age groups, however, frequently reported AEs were similar. In the 34 patients ≥ 65 years of age from the VDZ/VDZ group, arthralgia and headache were reported most commonly, and of these, only arthralgia was reported more commonly in the VDZ/VDZ group compared to placebo [n = 8 (24%) vs. n = 4 (18%), respectively]. Similarly, meaningful treatment group comparisons across race subgroups were unfeasible, given the low number of patients who were identified as Asian, Black, and Other races.

Analysis of safety by sex did not show any clear increased risk for AEs by sex with vedolizumab treatment. Headaches, arthralgia, and Crohn's disease were reported more frequently in females than in males (≥ 3% difference) in the combined vedolizumab group, but were also reported more frequently in females than males in the non-ITT placebo population. AEs reported by ≥ 10% of males or females in any treatment group were similar and are summarized in Table 77 below. No signal of increased risk for an AE or type of AE was observed when assessing AEs by weight or disease activity, and there were insufficient numbers of patients with creatinine clearance < 60 for meaningful comparisons to patients with normal renal function.

Table 77: AEs Reported by ≥ 10% of males or females in any treatment group, summarized by sex

	Female			Male		
Preferred Term, n (%)	VDZ/PBO N = 138	PBO/PBO N = 136	VDZ/VDZ N = 691	VDZ/PBO N = 141	PBO/PBO N = 161	VDZ/VDZ N = 743
Patients with at least 1 AE	115 (83)	117 (86)	613 (89)	119 (84)	115 (71)	590 (79)
Nasopharyngitis	16 (12)	10 (7)	84 (12)	13 (9)	11 (7)	96 (13)
Headache	28 (20)	21 (15)	105 (15)	15 (11)	11 (7)	72 (10)
Arthralgia	18 (13)	21 (15)	92 (13)	18 (13)	8 (5)	74 (10)
Crohn's Disease	18 (13)	27 (20)	96 (14)	11 (8)	9 (6)	68 (9)
Nausea	19 (14)	14 (10)	86 (12)	7 (5)	9 (6)	42 (6)
Pyrexia	20 (14)	14 (10)	64 (9)	10 (7)	8 (5)	63 (8)
Abdominal pain	13 (9)	18 (13)	65 (9)	7 (5)	11 (7)	49 (7)
Upper respiratory tract infection	9 (7)	12 (9)	64 (9)	10 (7)	7 (4)	42 (6)
Ulcerative colitis	12 (9)	15 (11)	43(6)	17 (12)	14 (9)	54 (7)

Source: Sponsor Submission, Integrated Summary of Safety, page 404 Table 7-8

The applicant also analyzed the safety datasets by patient geographic region, prior TNFα antagonist use, and baseline concomitant immunomodulator and corticosteroid use. Patients were categorized by the following geographic regions: North America, Western/Northern Europe, Africa/Asia/Australia, and Central Europe. Slight differences were noted in the frequency of AEs among patients in the VDZ/VDZ group across

geographic region; however, the rates of AEs in the placebo group by geographic region were similar (Africa/Asia/Australia 82% VDZ, 82% PBO; Central Europe 73% VDZ, 71% PBO; North America 88% VDZ, 84% PBO; and Central Europe 91% VDZ, 92% PBO). No clinically significant difference in the frequency of commonly reported AEs was seen among the PBO/PBO, VDZ/PBO, and VDZ/VDZ groups.

A larger proportion of patients with a history of TNFα antagonist use reported an AE than patients without a history of use. However, rates of AEs were similar across treatment groups when assessed by history of previous TNFα antagonist use. AEs reported by ≥ 10% of patients in any treatment group by history of previous TNFα antagonist use are summarized below. Rates of SAEs were similar in the subgroup of patients with previous use, compared to the overall study population. See section 1.3.2 for additional information on SAEs in this subgroup of patients.

Table 78: Adverse Events Reported by ≥ 10% of patients in any treatment group, summarized by prior TNFα Use

	No Prior TNFα Use			Prior TNFα Use		
Preferred Term, n (%)	**VDZ/PBO N = 150**	**PBO/PBO N = 152**	**VDZ/VDZ N = 588**	**VDZ/PBO N = 129**	**PBO/PBO N = 145**	**VDZ/VDZ N = 846**
Patients with at least 1 AE	118 (79)	115 (76)	451 (77)	116 (90)	117 (81)	752 (89)
Nasopharyngitis	12 (8)	9 (6)	54 (9)	17 (13)	12 (8)	126 (15)
Headache	17 (11)	12 (8)	63 (11)	26 (20)	20 (14)	114 (13)
Arthralgia	11 (7)	12 (8)	50 (9)	25 (19)	17 (12)	116 (14)
Crohn's Disease	12 (9)	7 (5)	40 (7)	17 (13)	29 (20)	124 (15)
Nausea	11 (7)	10 (7)	28 (5)	15 (12)	13 (9)	100 (12)
Pyrexia	13 (9)	10 (7)	39 (7)	17 (13)	12 (8)	88 (10)
Abdominal pain	7 (5)	13 (9)	46 (8)	13 (10)	16 (110	68 (9)
Upper respiratory tract infection	6 (4)	9 (6)	41 (7)	13 (10)	10 (7)	65 (8)
Ulcerative colitis	19 (13)	16 (11)	36 (6)	10 (8)	13 (9)	61 (7)

Source: Sponsor Submission, Integrated Summary of Safety, page 415 - 416

AEs reported by ≥ 10% of patients in any treatment group were similar when assessed by baseline immunomodulator and/or corticosteroid use and included nasopharyngitis, headache, Crohn's disease, arthralgia, abdominal pain, upper respiratory tract infection, pyrexia, and ulcerative colitis. There were no significant differences in commonly reported AEs among treatment groups, nor was a signal of increased risk for an AE observed when assessing AEs by baseline concomitant drug use.

Reviewer Comment: This reviewer saw no apparent signals for increased risk for an AE or any type of AE when assessing AEs by a variety of demographic factors, including age, sex, geographic region, and prior treatments. While there appeared to be an increased proportion of AEs in patients with previous TNFα use, the rates of AEs were similar across treatment groups in this subset, suggesting patients with previous TNFα use may have more serious underlying disease and/or a higher baseline risk for AEs.

7.5.4 Drug-Disease Interactions

The safety evaluation included an evaluation controlling for baseline disease severity. There were insufficient patients with creatinine clearance < 60 mL/min to allow meaningful comparison.

There is the potential that disease improvement can impact CYP450 and thus lead to disease-drug-drug interactions. This was not thoroughly explored in the clinical development program and may be considered in a PMC. *See the Clinical Pharmacology review for additional information.*

7.5.5 Drug-Drug Interactions

Monoclonal antibody-drug interactions are not common and when they occur are likely from overlaps in the mechanism of action, alteration in target, or drug-disease interaction. In addition, monoclonal antibodies that modulate cytokine production may affect the regulation pathways of P450 enzymes. Vedolizumab was not found to modulate cytokine production in in vitro and clinical studies.

No adverse events were observed that were assessed as related to drug-drug interactions.

Reviewer comment: The risk of drug-drug interactions is low with vedolizumab, given it is an antibody and interacts only with integrin receptors. Nothing was observed during the clinical development program. See the clinical pharmacology review for additional information on drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See section 7.3.5 Submission Specific Primary Safety Concern

7.6.2 Human Reproduction and Pregnancy Data

No evidence of fetal harm from vedolizumab was found in nonclinical reproduction studies in New Zealand white rabbits and Cynomolgus monkeys, at doses up to 25 times the human dose. No adequate and well controlled studies of vedolizumab were performed in pregnant women.

Reviewer comment: the applicant proposes Pregnancy Category B based on the nonclinical data and lack of clinical data supporting vedolizumab's safety in pregnant women. This is appropriate. Lactation studies should be performed as a postmarketing requirement.

7.6.3 Pediatrics and Assessment of Effects on Growth

This drug has not yet been studied in children. The applicant has requested a Waiver of Pediatric Study for pediatric patients from birth to (b) (4) and a Deferral of Pediatric Study for pediatric patients (b) (4).

Reviewer comment: The applicants waiver and deferral request appear appropriate to this reviewer. We generally have waived requirements for pediatric studies of UC treatments in children under the age of 5 years due to the low UC incidence in that age group; however, inclusion of patients as young as (b) (4) of age in your pediatric plan is acceptable. The final determination of waiver and deferral will be made upon presentation to the Pediatric Research Committee (PeRC) in January, and an addendum to my review will be provided, as necessary.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdosage reported in the vedolizumab clinical development program. Doses up to 10 mg/kg (approximately 2.5 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity.

7.7 Additional Submissions / Safety Issues

Study C13012 was a Phase 1 single-arm study to evaluate the effects of a single 450-mg IV dose of vedolizumab on the CD4:CD8 lymphocyte ratio in the CSF of healthy subjects. In a previous study of MS patients, natalizumab was shown to reduce the CSF CD4+:CD8+ lymphocyte ratio to a mean of 0.5. By contrast, MS patients not treated with natalizumab had a mean CSF CD4:CD8 ratio of 3.7. *(Stuve O, et.al., altered CD4:CD8 t-cell ratios in CSF of natalizumab treated patients with MS. Archives of neurology 2006;63(10):1383-7)* It has been hypothesized that natalizumab's effects on the ingress of leukocytes into the CNS and the lymphocyte ratio increases the risk of PML in natalizumab treated patients, so the applicant sought to assess the impact of vedolizumab on the CNS CD4+:CD8+ lymphocyte ratio.

Fourteen healthy adults ages 18-45 underwent a lumbar puncture before and after receiving a single 450-mg IV dose of vedolizumab. Subjects underwent a baseline LP at screening. If the screening CSF sample met study criteria for eligibility, the subject

was considered eligible and would be administered a single dose of vedolizumab within 2 to 10 days of the screening LP. A second LP was obtained 5 weeks after the dose of vedolizumab, and subjects were followed by telephone contact 6 months after dosing to determine if PML or malignancies had been diagnosed. Each subject served as his or her own control.

One patient had detectable HAHA at Week 5 and 16, so 13 subjects were included in the evaluable population for analyses of CSF endpoints. The mean CD4+:CD8+ ratios were 3.59 at baseline and 3.61 after dosing for a mean difference of 0.013 (90% CI: -0.337, 0.363). In addition, no subject had a post dose CD4+:CD8+ ratio of less than 1. In Study C13012, vedolizumab did not affect CD4+ cell counts, CD8+ cell counts, or CD4+:CD8+ ratio in the CSF of humans. These results are consistent with nonclinical studies of vedolizumab in rhesus monkeys.

8 Postmarket Experience

There is no postmarket experience with this drug because it is not approved at the time of this review.

9 Appendices

9.1 Literature Review/References

See footnotes.

9.2 Labeling Recommendations

The Applicant's proposed label included all the required sections and was appropriately formatted. The Applicant's proposed label was reviewed, and revisions and comments will be communicated to the Applicant on November 20, 2013.

Major clinical issues related to the label included:

- Revisions were made to the indication based on clinical trial findings, specifically the indication of mucosal healing was changed to "improved endoscopic appearance of the mucosa"
- Specific information was added in *5 Warnings and Precautions* that anaphylaxis has been reported with ENTYVIO administration
- Specific information was added in *5 Warnings and Precautions* that serious infections have been reported in patients treated with ENTYVIO
- The immunogenicity of vedolizumab was underestimated in the label, and significant revisions to this section will be communicated to the Applicant
- Revisions were made to section 12.1 Mechanism of Action to remove language indicating that vedolizumab is (b) (4) and to provide more detailed information on its relative (b) (4)
- Revisions were made to section 14.1 ulcerative colitis clinical studies:
    - Clarifying, when necessary, the differences between the US population and the population outside the US
    - Treatment differences and confidence intervals added
    - All text providing results from (b) (4) was removed

All labeling recommendations are subject to formal negotiations with the Applicant. The final approved labeling will be appended to the approval letter.

9.3 Advisory Committee Meeting

An FDA Advisory Committee Meeting is scheduled for December 9, 2013. The results of that meeting will be provided as an addendum to this review.

9.4 Detailed Events of Pre-submission Regulatory History

June 7, 2000: Original IND submission – IND 009125

June 22, 2004: This was a Type C meeting to discuss the development of MLN02, including switching to a CHO cell line and anti-MLN02 antibodies (HAHA). FDA recommended additional dose exploration before proceeding to Phase 3. Millenium will continue with two phase 2 studies, M200-021 and L299-016, exploring dosing up to 10mg/kg.

January 24, 2006: IND 009125 was placed on clinical hold for insufficient information to allow the Agency to assess the risk of progressive multifocal leukoencephalopathy (PML) to subjects with MLN02. The clinical hold was prompted by fatal cases of PML reported with Tysabri® (natalizumab), a monoclonal antibody with a similar mechanism of action as MLN02.

April 4, 2006: This was a Type A meeting to discuss options for removing the clinical hold. Discussion focused on PML risk minimization and safety monitoring. Specific agreements included:

- FDA emphasized the need for 2 years of follow-up in the post exposure period, even in patients who drop out of the study or are lost to follow up. Millenium agreed to call subjects by phone every six months until 2 years after treatment discontinuation.
- A risk minimization plan, including education of site personnel and patients, follow-up of patients, and retrospective analysis of patient sera for JC virus, is necessary for all future studies, including Phase 1 bridging studies.
- A detailed Phase 3 plan and protocols, including specific safety monitoring plans for PML, should be submitted as a complete response, for consideration in removing the clinical hold. The final decision will be based on a review of the submission addressing the clinical hold issues.
- The sponsor was also requested to provide a retrospective analysis of all neurological adverse events to date with the drug product

July 26, 2006: This was a Type C meeting to discuss changes to the manufacturing process. Discussion focused on manufacturing changes from MLN02 (Process A), an NSO cell line-derived monoclonal antibody to MLN0002 (Process B), a CHO cell line-derived monoclonal antibody, and the impact of these changes on the development program. Specific clinical comments included:

- The Agency was unable to comment in detail the proposed Phase 3 development plans and specific study design issues. Several differences were noted between the completed Phase 2 Study using MLN02 and the proposed new Phase 1 bridging studies. Specifically, the use of more severe UC patients in proposed Phase 1 Study Ab than in the prior Phase 2 study. In addition, the doses and dosing regimen for the proposed Phase 1 studies were different. Millenium

stated that the dosing would be based on the need to maintain (b) (4) saturation of cellular binding sites, which correlates directly with efficacy.

June 18, 2007: The sponsor submitted an amendment which was a complete response to the clinical hold.

July 19, 2007: The Agency issued a letter removing the clinical hold on IND 9125 based on additional safety measures being implemented related to potential PML risk.

December 11, 2007: This was a Type C meeting to continue discussion about a PML risk management plan.

- The Agency stated that patients should not receive concomitant immunosuppressants while being treated in the study, and patients should be tapered off of corticosteroids within six months of starting study treatment.
- The appropriate patient population to enroll is those who have failed or cannot tolerate immunosuppressive therapy and at least one TNF blocker.
- Patients who have a positive JC virus DNA test on screening should be excluded from the study
- Agency agreed that routine screening and monitoring MRIs would not be required on all patients, provided patients have a screening baseline neurologic exam with exclusion of those with abnormal findings. Agency also agreed that routine neurological exams did not have to be completed by a neurologist.

April 18, 2008: This was a Type C meeting to discuss MLN0002's overall development program, with an approach to comparability, dose selection, and outstanding issues regarding nonclinical requirements.

June 5, 2008: The purpose of this Type C, End of Phase 2 meeting was to discuss pivotal studies that support the proposed IBD program for MLN0002.

- The Agency recommended that an additional adequate and well-controlled induction study be conducted for UC and CD.
- The Agency recommended that the criteria for "failure" (had inadequate response, lost response, or was intolerant) to each specific agent (e.g., steroids, immunosuppressants, or TNFα antagonists) be tailored, and that the dose and duration of that agent that must be tried to be considered an adequate trial be specified.

September 16, 2008: This was a Type B, End of Phase 2 meeting to discuss specific CMC plans and protocols for Phase 3 activities and to evaluate data demonstrating comparability of the Phase 2 (Process B) drug substance and drug product and the Phase 3 (Process C) drug substance and drug product. Specific agreements from this meeting included:

- FDA generally agreed with the development plans to introduce MLN002 Process C material into the Phase 3 clinical studies. Specifically, FDA agreed that

Millennium had demonstrated sufficient viral safety to allow initiation of Phase 3 trials and that plans for validating viral clearance should be sufficient for registration purposes.

- (b) (4) .
- FDA acknowledged receipt of a PK/PD comparability study to compare Process B and C products

September 26, 2008: This was a Type C, End of Phase 2 teleconference to discuss outstanding clinical questions and issues for Phase 3 activities. The following agreements were made during this meeting:

- The Agency agreed to allow concomitant steroid use for one and one-half years, with tapering at week 6 in Study C13006 in patients that are in clinical response, or when clinical response is achieved, and to allow concomitant immunosuppressant use for up to 6 weeks, provided that immunosuppressant use will be otherwise prohibited. These agreements required the selection criteria for prior use of conventional therapies be modified so patients enrolled meet the stricter requirement of inadequate response or intolerance to immunosuppressants or TNFα antagonists, rather than immunosuppressants, TNFα antagonists, or corticosteroids.

September 10, 2009: The purpose of this Type C meeting was to discuss the statistical analysis plan for the Phase 3 Crohn's Disease study, C13007.

July 13, 2010: The purpose of this Type C meeting was to discuss Phase 3 clinical development plans for ulcerative colitis and Crohn's disease. Specific discussion related to UC included:

- Millennium requested that the FDA allow concomitant use of immunomodulators throughout Phase 3 studies, and allow inclusion of patients in the US have may have failed immunomodulators, TNFα antagonists, or corticosteroids, in order to harmonize global enrollment criteria. The Agency maintained its previous position
  - continue to require limiting of concomitant immunosuppressants for 6 weeks and steroids for one and one-half years, provided that patients in clinical response are tapered from steroids at Week 6 or at the subsequent visit when clinical response is achieved.
  - continue requirement of inadequate response or intolerance to immunosuppressants or TNFα antagonists, only, for inclusion
- Millenium requested clarification on the number of patients needed in their safety database for BLA filing. The Agency reiterated Millennium would need 3000 patients for an average duration of exposure of 18 months to define the risk of PML associated with vedolizumab, and to provide data that the mechanism of action has the potential to result in less risk of PML than natalizumab.

- Millenium summarized that the MLN002 development program for UC includes 1 large, adequate and well-controlled study (C13006) for the induction and maintenance of clinical response and remission in patients with moderately to severely active UC. The Agency strongly recommended two adequate and well controlled clinical trials and referred the sponsor to "*Guidance for Industry-Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."* In order to consider 1 study, the Agency recommended the studywise Type I error rate be 0.001 or less and the effect size would need to be clinically relevant and meaningful. In addition, the study would need to meet the following requirements:
    - no single study/site provides an unusually large fraction of patients
    - no single investigatory or site provides a disproportionate favorable effect
    - multiple endpoints involving different events
    - statistically very persuasive findings

July 20, 2011: Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The purpose of this closed session Advisory committee was to seek the committee's recommendations regarding the phase 3 study design for vedolizumab, including the number of patients and duration of study needed to exclude the risk of PML. Below are the questions asked of the advisory committee, including voting results and a summary of responses.

- **Nonclinical Data/Human Pharmacodynamic Data:** Do the nonclinical data (e.g., specific α4β7 receptor binding target) and the human pharmacodynamic data presented for vedolizumab provide assurance of less risk of PML than natalizumab?

  Voting Results: YES: 5 NO: 12 ABSTAIN: 1

  The committee did not unanimously agree on this question. Those who voted "yes" were swayed by the possibility that there could be a different mechanism of action for vedolizumab, T-cell trafficking maintained in the CNS, and the adaptive immune response against the JC virus. The members who voted "no" struggled with the strength of the word "assurance" and would like to see clinical data support animal data. They also commented that in vitro data cannot be extrapolated to human responses in clinical trials. One member abstained due to the wording of "assurance" in the question.

- **Safety Database:** Comment on the number of patients and duration of exposure to vedolizumab that would provide an acceptable pre-approval assessment of PML risk in patients with Crohn's disease and ulcerative colitis. In your answer, consider the number of patients available for analysis receiving, and not receiving, concomitant immunosuppressants.

  This was a non-voting question.

The majority of the committee felt that increasing the sample size has merit. Some commented that the range should be about 2000 to 3000 patients. They also strongly expressed that the duration is extremely important and that 18 months may be too short of a timeframe and that possibly 24 months may be the minimum duration timeframe. In regards to concomitant immunosuppressants, the committee felt that it is a confounding factor which may not likely allow for decreasing the sample size. Lastly, the committee agreed on the important point of having an aggressive post-marketing program to keep track of PML risks.

- **Entry Criteria:** In the current US protocols, only patients with inadequate response or intolerance to TNFα-antagonists or immunosuppressants are allowed to enroll.

  Do the available nonclinical and clinical data support making the entry criteria less stringent (i.e., allow entry of patients that have not yet been treated with TNFα-antagonists or immunosuppressants)?

  Voting Results: YES: 2 NO: 15 ABSTAIN: 1

  The overall majority of the committee felt that the nonclinical and clinical data do not support making the entry criteria less stringent. They felt that there are safer, effective drugs to use as first line agents and that this drug should be considered as a second to third line agent. They also felt that the efficacy of the drug is not proven and that the toxicity of the drug is not fully understood, thus the protocol should not be altered.

  The panel members who voted "yes" expressed that prior use of these drugs increased risks for PML and did not understand the rationale for allowing only patients with prior use of these drugs to enroll. One committee member abstained from voting because she felt that there is not enough clinical context to a make a decision and more data are needed.

- **On-study Restrictions:** In the current US protocols, concomitant immunosuppressants are prohibited beyond the induction phase of vedolizumab treatment. Do the available nonclinical and clinical data support making these restrictions less stringent (i.e., allow concomitant immunosuppressants throughout induction and maintenance treatment)?

  Voting Results: YES: 0 NO: 17 ABSTAIN: 1

  The overall majority of the committee agreed that concomitant immunosuppressant restrictions should not be less stringent. They felt that concomitant immunosuppressants would confound the trials even more and may pose an increased risk of complications.

  The one panel member abstained from voting and felt that the question was beyond his expertise and knowledge.

September 6, 2011: This Type C meeting was as a follow up to the Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The purpose of this meeting was to discuss the outcomes of the Advisory Committee meeting and discuss the next step in the development program for MLN0002.

- The Division recommended Millennium should study at least 1,000 patients for a minimum number of 24 infusions. With this safety database, the 95% CI upper bound for the true PML event rate after 24 or more infusions would be 3/1000 (based on the Rule of 3) if no events are observed. The Division believes that since a substantial proportion of patients in the maintenance phase will be receiving Q8 weeks treatment, basing the safety database on number of infusions is more appropriate than months of exposure (if the Q4 weeks treatment was the approved dose, an inadequate number of patients treated at that dose may be in the safety database at the time of the BLA filing if the number is based on months of exposure rather than number of infusions). Millennium believed that analysis of the safety database using number of infusions, rather than months of exposure, is inappropriate. FDA agreed to have further discussion on this, as well as Millennium concerns regarding the inclusion of the risk of PML in the label and a risk management program, at the Pre-BLA meeting.
- The Agency and Millennium agreed that JC viremia has been demonstrated to be unlikely of use as a predictor of PML risk in patients treated with natalizumab and that it is acceptable to discontinue JC virus measurements in serum in vedolizumab clinical trials.

July 24-25, 2012: This was a Type C, End of Phase 3 meeting to discuss the clinical development plan to support registration of vedolizumab for the treatment of ulcerative colitis and Crohn's disease. There were four major goals of the meeting: 1) Review key clinical analyses data from the completed UC and CD phase 3 studies and obtain concurrence that there is substantial evidence of efficacy in patients with either moderately to severely active UC and CD; 2) obtain concurrence on the suitability of measuring patient exposure to VZB in terms of months as opposed to number of infusions; 3) discuss a proposed pharmacovigilance and risk management plan to be implemented post approval; 4) discuss the proposed data format for the BLA clinical and nonclinical datasets. Major discussion points related to the UC development plan included:

- The Agency could not agree that the treatment effect from the Phase 3 Induction Study C13006 meets the criteria for substantial evidence of efficacy based on a single adequate and well-controlled trial and stated this is a review issue. The requirements for demonstration of efficacy from a single study include: statistically very persuasive findings, an effect size that is clinically relevant and meaningful, results that are internally consistent across multiple endpoints, centers, subgroups, and countries.

- A single adequate and well-controlled maintenance study could be sufficient to extend a claim to maintenance in a population, if there is substantial evidence of efficacy for induction in that population.
- The Agency noted that patients from two different cohorts enter into the maintenance study and requested that Millennium provide a separate analysis for each of the cohorts for the primary and secondary endpoints of the maintenance study
- A risk evaluation and mitigation strategy (REMS) may be necessary to ensure that the benefits of vedolizumab outweigh the risks. The Agency encouraged Millennium to submit proposed REMS with their application.
- The safety database was discussed further, with the Agency reiterating previous comments on the needed size of the safety database. In addition, the Agency stated that if Millenium's safety database at the time of BLA filing is less than 1000 patients exposed to ≥ 24 infusions (with a substantial proportion of these patients exposed to ≥ 36 infusions), it would be acceptable for additional data to be submitted as part of the Day 120 Safety Update Report (with a reasonable data cutoff date) to count towards the requirement of an adequate safety database at the time of BLA filing.
- In addition, the Division stated that they are currently re-evaluating endpoint definitions in UC and re-evaluating the requirements to support labeling claims for "mucosal healing" in UC (i.e., definitions, standardized endoscopy methodology, use of histology, etc).
- The sponsor indicated that clinical remission in Study C13006 is defined as total Mayo score of ≤ 2 and no individual sub score > 1. Additional analyses were requested using the following alternate definition of clinical remission: total Mayo score of ≤ 2 and no individual subscore > 1 where the Rectal Bleeding subscore must equal 0 and the Endoscopy subscore must equal 0.
- The Agency requested that exposure data be provided using both number of infusions and number of months and by categories of prior and concomitant immunosuppressant use.

November 6, 2012: The purpose of this Type B, Pre-BLA meeting was to discuss the content and format of a complete BLA for vedolizumab for the treatment of patients with moderately to severely active UC or CD, who have had an inadequate response with, lost response to, or were intolerant to 1 or more conventional therapies, including TNFα

- FDA stated that due to the new requirements under PDUFA V for applications under the "Program", the safety database at the time of original BLA submission must include data on at least 900 patients that received ≥ 24 infusions (with a minimum of 4 weeks of follow-up after the last infusion). These data cannot be provided in the 120-Day Safety Update report.
- The Agency agreed that a single ISS in the BLA to support the indications of UC and CD is appropriate, but that the safety analyses must also be presented by individual indication. Similarly, submission of a single Section 2.7.4 Summary of

Clinical Safety (SCS), which will contain safety information for both UC and CD, separately and in aggregate, is acceptable.

- The Agency acknowledged that Millennium would not be submitting a PRO dossier with this application to support the patient components of the Mayo scoring system.
- The sponsors plans to request a deferral of clinical investigation in children between (b) (4) years of age until the post marketing period and a waiver of studies in children (b) (4) years of age appears reasonable but will be subject to review by the Office of New Drugs Pediatric Review Committee (PeRC)
- The Agency encouraged the completion of subgroup analyses of patients who have received concomitant corticosteroids or immunomodulators, however, it is unlikely that this will be sufficient to support a specific (b) (4) of the safety and efficacy of vedolizumab with these concomitant medications. Such a claim would generally require an experimental design that is specific to answer that question, rather than an exploratory or subgroup analysis.
- The sponsor asked if the proposed analyses will provide sufficient data to support a review of the following proposed dosing regimen: *300 mg administered as an intravenous infusion over 30 minutes at Week 0, Week 2, Week 6, then every 8 weeks thereafter. If there is an inadequate response to the 300 mg every 8 weeks treatment and the treatment is well tolerated, then the treatment frequency may be increased to 300 mg every 4 weeks.* The Agency's current thinking was that the data are not sufficient to evaluate the efficacy of dose escalation in patients who had an inadequate response to the Q8 weeks regimen because patients who had an inadequate response in the study were not re-randomized to remaining on the Q8 weeks regimen vs escalation to the Q4 weeks regimen.

November 13, 2012: This was a Type B, Pre-BLA CMC only meeting where agreements were made on stability data submission, proposed release testing and acceptance criteria, the sponsor's approach for determining extractable/leachable information, and the sponsors proposal to include a (b) (4) of vedolizumab drug product manufacture at (b) (4)

February 21, 2013: Vedolizumab was granted fast track designation in the treatment of ulcerative colitis and Crohn's disease.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURIE B MULDOWNEY
11/20/2013

ANIL K RAJPAL
11/20/2013
I concur with Dr. Muldowney.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: BLA 125476 **Applicant: Takeda Pharmaceuticals U.S.A., Inc.** **Stamp Date: 20-Jun-2013**

Drug Name: vedolizumab **NDA/BLA Type: original submission**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD Format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Draft labeling provided consistent with requirements in 21CFR 201.56(d) and 201.57.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			The Summary of Clinical Safety references the ISS, agreed at preBLA mtg
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Applicant refers to Module 2.7.3, Summary of Clinical Efficacy – CD, agreed at preBLA mtg 21Feb2013
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Summarized in section 6 of Clinical overview (2.5)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA (section 351 of PHS Act)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Studies:** C13007, C13011 **Indication**: Adult Crohn's Disease Reducing signs and symptoms, inducing and maintaining clinical response and remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist.	X			For the CD indication two well controlled studies were submitted, C13007 covered both induction and maintenance, C13011 induction only.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			The US population had more restrictive eligibility criteria, specifically restricting the use of concomitant corticosteroids and immunosuppressive therapy, however, the US population met eligibility criteria reflective of the global UC population. "the US and non-US populations are clinically similar, the safety and efficacy results for each of the phase 3 studies were analyzed in the pooled study populations".
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Safety data presented by individual indication and then combined. agreed upon at preBLA mtg 06Nov13.
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Study C13009
20.	Has the applicant presented a safety assessment based on all	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 14.0 used
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives submitted for all pts who experienced ≥1 SAE, except for SAEs of disease exacerbation considered unrelated to study drug. agreed upon at preBLA mtg 06Nov13.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Additional safety data submitted as discussed at preBLA meeting on06Nov13.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			- waiver requested for patients (b) (4) years of age - deferral requested for patients (b) (4) years of age with suggested date for submission of pediatric phase 2 study protocol ~Sept 2014
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional case report forms requested by the Division.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			The sponsor provided a single FORM FDA 3454 with an appended list of investigator names from each covered study. No FORM FDA 3455s were provided.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Statement that studies were conducted consistent with GCP included on page 14 of clinical overview

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Klaus Gottlieb, MD, MS, MBA	19 August , 2013
Reviewing Medical Officer	Date
Anil Rajpal, MD, MPH	19 August, 2013
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KLAUS T GOTTLIEB
08/19/2013

ANIL K RAJPAL
08/19/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: BLA 125476 **Applicant: Millenium Pharmaceuticals, A Takeda Oncology Company** **Stamp Date: 20-Jun-2013**

Drug Name: vedolizumab **NDA/BLA Type: original submission**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD Format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			PLR format & c/w requirements in 21CFR 201.56(d) & 201.57.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			The Summary of Clinical Safety references the ISS - agreed at preBLA mtg
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Applicant refers to Module 2.7.3, Summary of Clinical Efficacy – UC, agreed at preBLA mtg 21Feb2013
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Summarized in Clinical overview (2.5)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA (section 351 of PHS Act)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			300mg IV at Week 0, 2, 6 and Q8W thereafter. Dose selection for

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: M200-022 **Study Title:** Phase 2, Randomized, Double-Blind, Placebo-Controlled Study **Sample Size:** 181 **Arms:** 3 (Placebo, 0.5 mg/kg, 2.0 mg/kg) **Location in submission:** 5.3.5.1 **Study Number**: C13002 **Study Title:** Phase 2, Randomized, Double-Blind, Placebo-Controlled PK/PD Study with Exploratory Efficacy Endpoints **Sample Size:** 46 **Arms:** 4 (Placebo, 2.0 mg/kg, 6.0 mg/kg, 10.0 mg/kg) **Location in submission:** 5.3.5.1				phase 3 was based on dose-response from M200-022 and C13002. Final dose recommendation for marketing was selected based on results from the C13006 maintenance study.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1:** C13006 **Indication:** for reducing signs and symptoms, inducing and maintaining clinical response and remission and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerateive colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist	X			1 adequate and well-controlled study provided for UC indication, however, his was discussed at the EOP 3 meeting on 24/25Jul12 as well as the preBLA. Determining whether the results meet the criteria for substantial evidence is a review issue.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		Definition for mucosal healing does not appear to be consistent with current thinking.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			The US population had more restrictive eligibility criteria, specifically restricting the use of concomitant corticosteroids and immunosuppressive therapy, however, the US population met eligibility criteria reflective of the global UC population. "the US and non-US populations are clinically similar, the safety and efficacy

	Content Parameter	Yes	No	NA	Comment
					results for each of the phase 3 studies were analyzed in the pooled study populations".
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			safety data presented by individual indication and then combined. agreed upon at preBLA mtg 06Nov13.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Study C13009
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 14.0 used
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			narratives submitted for all pts who experienced ≥1 SAE, except for SAEs of disease exacerbation considered unrelated to study drug. agreed upon at preBLA mtg 06Nov13.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Additional safety data submitted as discussed at preBLA meeting on06Nov13.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*,			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			- waiver requested for patients (b) (4) years of age - deferral requested for patients (b) (4) years of age with suggested date for submission of pediatric phase 2 study protocol ~Sept 2014
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			see comment for 17 above.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional case report forms requested by the Division.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			The sponsor provided a single FORM FDA 3454 with an appended list of investigator names from each covered study. No FORM FDA 3455s were provided.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes___

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

n/a

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

information requests:

- missing EPOCH variable
- additional analyses related to proposed secondary endpoint of corticosteroid-free remission – analysis of proportion of patients who are corticosteroid-free, by treatment arm, regardless of remission status AND descriptive statistics showing the duration of time patients in each treatment arm were corticosteroid free for the maintenance phase
- sensitivity analyses for primary efficacy endpoints on the per protocol population, excluding patients who did not meet eligibility criteria

Laurie Muldowney, MD

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURIE B MULDOWNEY
07/30/2013

ANIL K RAJPAL
08/09/2013