CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125476Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 20, 2014
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	BLA 125476
Applicant	Takeda Pharmaceuticals U.S.A., Inc.
Date of Submission	June 20, 2013
PDUFA Goal Date	May 20, 2014 (includes 3-month extension due to Major Amendment)
Proprietary Name / Established (USAN) names	Entyvio / vedolizumab
Dosage forms / Strength	Lyophilized Powder for Injection
Proposed Indications	1. Moderate to Severe Ulcerative Colitis (Induction and Maintenance) 2. Moderate to Severe Crohn's Disease (Induction and Maintenance)
Recommended Action:	Approval

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1. Introduction

This submission, received June 20, 2013, is the initial Biologics License Application (BLA) for Entyvio (vedolizumab), a humanized monoclonal antibody that specifically binds the α4β7 integrin. The Applicant is Takeda Pharmaceuticals U.S.A., Inc.

The Applicant proposes the following indications for ulcerative colitis (UC) and Crohn's disease (CD):

- UC: "…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 a tumor necrosis factor-alpha (TNFα) antagonist."

- CD: "…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."

2. Background

2.1. Potential Risk of PML

Although there were no PML cases in the vedolizumab clinical development program, there is concern about the risk of PML with vedolizumab because its purported mechanism of action (disruption of integrin function) is similar to that of natalizumab, a product that has been associated with PML. It should be noted that with natalizumab, longer treatment duration (particularly greater than 24 months), prior treatment with an immunosuppressant, and presence of anti-JCV antibodies are associated with increased risk of PML. However, for vedolizumab, the risk factors for the potential risk of PML are not known at this time as no cases have been reported in patients taking vedolizumab.

The Applicant asserts that vedolizumab does not have the same risk of PML as natalizumab because of mechanistic differences between the two products (mainly differences in receptor binding targets), and that *in vitro* activity data, animal models, and human pharmacodynamic (PD) data suggest a lower PML risk than for natalizumab.

2.2. Approach to Risk Evaluation and Management in Vedolizumab Clinical Trials

The key elements of the Division's approach to managing the potential risk of PML in the vedolizumab clinical trials was to select an appropriate study population (one for whom the potential risk of PML would be more acceptable) and to limit concomitant immunosuppressive therapies during the trials (because of concerns of increased risk with concomitant immunosuppression). The Division required (in the US version of the protocols) that patient enrollment be limited to patients who failed immunosuppressants or TNFα antagonists (patients who failed steroids only could not enter the trials), and that concomitant immunosuppressants be limited to the induction phase only.

Other key protocol requirements that were aimed at evaluating and managing the potential risk of PML included neurological examinations (baseline and periodically during and after the study), a case evaluation algorithm for suspected PML (that included referral to a panel of PML experts), and post-study follow-up for two years. There were also requirements for informed consent of subjects, and for education of subjects and site personnel. Many of these features were implemented by the Applicant in the Risk Assessment and Minimization for PML (RAMP) Program.

2.3. Ulcerative Colitis

Ulcerative Colitis

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but age of onset can vary widely. UC is more common in whites vs. non-whites and in women vs. men. The disease is manifest as mucosal inflammation and mucosal ulceration that occurs in the colon in a continuous segment beginning with the rectum. Extent of involvement varies, but it can include the entire colon. Involved areas classically show inflammatory changes that are limited to the mucosa, and, depending on severity, there may be extensive, broad-based ulceration.

Clinically, UC presents as a chronic relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain, but there may be long quiescent periods between attacks. There may also be systemic manifestations of the disease, with involvement of joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a very significant risk of colon cancer with longstanding disease, such that pancolitis of 10 years duration or longer has a 20- to 30-fold increased risk of cancer compared to the general population. Surveillance colonoscopies for patients at higher risk are routinely offered.

Current Treatment Options for Ulcerative Colitis

Decisions about treatment of UC weigh such factors as disease activity, disease extent and duration, previous treatment attempts and the patient's preference. The goal is to stop the patient's active acute disease (induction of remission) and then maintain the patient in remission.

Aminosalicylate preparations, given orally, rectally or in combination, are the first line of treatment for induction of remission (aminosalicylates are approved to treat mildly or moderately active UC including, for certain products, maintenance of remission). Patients with mild-to-moderate UC that is refractory to aminosalicylates are often advanced to oral corticosteroids (approved to "tide the patient over a critical period") and immunosuppressive agents (e.g., azathioprine or 6-mercaptopurine; widely used but unapproved). Use of any of the preceding has come to be considered part of "conventional therapy."

Currently, Remicade (infliximab), Humira (adalimumab), and Simponi (golimumab) are the only TNFα-antagonists approved for induction and maintenance of remission in patients with moderately to severely active UC who have inadequate response to conventional therapy.

Remicade, Humira, and Simponi have been shown to be effective in this population and have an acceptable safety profile; however, many patients do not respond initially, lose response over time, and/or develop intolerance.

Colectomy is still required for many when medical therapy fails or when epithelial dysplasia is found on surveillance. Total proctocolectomy with ileal pouch–anal anastomosis (IPAA) is currently the procedure of choice because it preserves anal sphincter function. While the mortality of the procedure is low, long-term morbidity is not. Pouchitis, often intermittent and recurrent, is a prevalent problem with symptoms that include increased stool frequency, urgency, incontinence, seepage, and abdominal and perianal discomfort.

2.4. Crohn's Disease

Crohn's Disease:

Crohn's disease (CD), also known as regional enteritis, terminal ileitis, or granulomatous colitis, is an inflammatory bowel disease of unknown etiology. The disease is manifest as discontinuous transmural inflammatory changes that can occur anywhere in the GI tract but it primarily involves small bowel or colon. Involved areas classically show noncaseating granulomas and fissuring. Complications include strictures, obstruction, malabsorption, malnutrition, and fistula formation. Growth retardation is a complication of concern in pediatric patients. There is an increased risk of malignancy with longstanding disease. Peak ages of diagnosis are the teens to twenties, but it can occur at any age.

Current Treatment Options for Crohn's Disease:

Decisions about treatment of CD weigh such factors as disease activity, disease extent and duration, previous treatment attempts and the patient's preference. The goal is to stop the patient's active acute disease (induction of remission) and then maintain the patient in remission.

Approved therapies for Crohn's disease include formulations of oral and IV steroids. Commonly used, but unapproved, therapies are aminosalicylates, azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX). Use of any of the preceding has come to be considered part of "conventional therapy" for the disease.

Currently, Remicade (infliximab), Humira (adalimumab), and Cimzia (certolizumab) are the only TNFα-antagonists approved for induction and maintenance of remission in patients with moderately to severely active Crohn's disease with inadequate response to conventional therapy. Remicade, Cimzia, and Humira have been shown to be effective in this population and have an acceptable safety profile; however, many patients do not respond initially, lose response over time, and/or develop intolerance.

Tysabri (natalizumab) is an integrin antagonist approved for moderately to severely active CD with an indication limited to patients that have failed conventional therapy and TNFα-antagonists. Because of the risk of PML, Tysabri is available only through a special

restricted distribution program called the CD TOUCH program. The number of patients that have received Tysabri for CD is very small (approximately 1,100).

2.5. Regulatory History

2.5.1 Overview of Regulatory Activity

The table below provides an overview of the regulatory activity of vedolizumab prior to submission of the BLA.

Table 1. Pertinent Regulatory History of Vedolizumab (BLA 125476)*

Date	Event
June 7, 2000	Initial IND submission (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.

Date	Event
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.

The table above is modified from the Clinical Review by Laurie Muldowney
*IND 9125

2.5.2 Key Comments Communicated to the Sponsor

Key comments communicated to the sponsor during the meetings and review of the IND submission included the following:

Management and Assessment of the Risk of PML:

The following major agreements were made relating to the management and assessment of the risk of PML with this product:

- Entry 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 inadequate response or intolerance to immunosuppressants, TNFα antagonists, or corticosteroids).
- Concomitant Immunosuppressive Therapies: Concomitant immunosuppressant and corticosteroid use was limited during the clinical trials. Concomitant immunosuppressants were limited to the induction phase only (e.g., six weeks). There were protocol-defined provisions to mandate tapering of corticosteroids after six weeks in patients that were in clinical response or at the subsequent visit when clinical response was achieved, and to limit corticosteroid dose increases to no greater than baseline dose; there were specified maximum steroid doses allowed on entry into the study.
- Informed Consent / Education of Subjects and Site Personnel: Subjects were to be advised of the risks of PML, how to recognize symptoms of possible PML, and who to contact should they experience symptoms suggestive of PML. Prior to the start of the study, investigators and site staff must have been provided with education about the signs and symptoms of PML, and the procedures to follow if a case of PML was suspected.
- Neurological Examinations: Neurological examinations were to be conducted at entry with exclusion of patients with an abnormal finding. Follow-up neurologic exams were to be conducted approximately every three months while on treatment, and approximately three months after stopping treatment.
- PML Case Evaluation Algorithm: There was a PML case evaluation algorithm that indicated what further studies were to be conducted if a physician could not rule out PML. If, after further testing, PML still could not be ruled out, the subject was to be referred to an outside panel of PML experts, including at least one neurologist, for final determination of whether or not the subject had PML.

- Post-study Follow-up: Subjects were to be followed for two years after treatment was completed. Interim assessments were at 3, 6, 12, and 18 months. Subjects were to be questioned regarding the presence of any signs or symptoms of opportunistic infections and PML. Any positive findings on questioning were to be expeditiously referred to a physician for additional evaluation, and the PML case evaluation algorithm followed.
- Safety Database: The safety database at the time of original BLA submission was required to include data on at least 900 patients that received ≥ 24 infusions, with a minimum of 4 weeks of follow-up after the last infusion (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).

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.

Efficacy Standard (for Induction and Maintenance Indications):

The following efficacy standard (for induction and maintenance indications) was communicated to the Applicant (for each disease population - UC and CD):

- Induction: "To provide substantial evidence of efficacy for induction in one disease population (e.g., either UC or CD), we recommend that you plan to conduct two adequate and well-controlled induction studies in that population for which you seek an indication."
- Maintenance: "If you have substantial evidence of efficacy for induction in a population, then a single adequate and well-controlled successful maintenance study in that population could be sufficient to extend the claim to maintenance in that population."

See the Clinical Reviews by Laurie Muldowney and Klaus Gottlieb for details of the vedolizumab regulatory history.

2.6 Current Application

The application was submitted on June 20, 2013. It was classified as a Priority submission with a PDUFA deadline of February 20, 2014. Because of a major amendment received on December 6, 2013, the PDUFA date was extended to May 20, 2014.

2.6.1 Advisory Committee

The application was presented to a joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee during the current review cycle (December 9, 2013) to seek recommendations on a number of issues. The issues and the corresponding recommendations were as follows:

- Evidence of efficacy for the CD induction indication: The majority (12 versus 9) voted that the data support the efficacy of vedolizumab for the proposed CD induction indication.

- Evidence of efficacy for the CD maintenance indication: Twenty members (with 1 abstaining) voted that the data support the efficacy of vedolizumab for the proposed CD maintenance indication.
- Adequate characterization of the potential risk of PML: All 21 members voted that the applicant has adequately characterized the potential risk of PML to support approval, but noted that continued monitoring and observation are still necessary to assess the potential risk of PML and the occurrence of serious infections.
- Requirement for concomitant immunosuppressants to be limited to a specific duration (e.g., during induction only): The majority (19 versus 1 with 1 abstaining) voted that concomitant immunosuppresants should not be limited to a specific duration.
- Benefit-Risk Assessment in UC: The majority (13 out of 21) voted that the benefits outweigh the risks in the proposed indicated population of UC patients that have failed steroids or immunosuppressants or TNF α-antagonists. The remaining eight members voted that the indicated population should not include patients that have failed steroids only.
- Benefit-Risk Assessment in CD: The majority (14 out of 21) voted that the benefits outweigh the risks in the proposed indicated population of CD patients that have failed steroids or immunosuppressants or TNF α-antagonists. Of the remaining seven members, six voted that the indicated population should not include patients that have failed steroids only, and one abstained.
- Safety and Risk Mitigation: Members commented that it is important to quantify PML risk and to monitor other infections in addition to PML, but noted that post-market risk mitigation strategies should not be burdensome for the practitioners.

2.6.2 Review Documents

The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

(1) Clinical Reviews:
   (a) Clinical Review by Laurie Muldowney (UC), dated November 20, 2013, and Addendum dated April 11, 2014
   (b) Clinical Review by Klaus Gottlieb (CD), dated December 30, 2013

(2) Statistics Reviews (Division of Biometrics III):
   (a) Primary Statistics Review by Milton Fan (UC), dated May 15, 2014
   (b) Primary Statistics Review by Milton Fan (CD), dated May 19, 2014
   (c) Secondary Statistics Memo (UC and CD) by Freda Cooner, dated May 19, 2014

(3) Safety Statistics Reviews (Division of Biometrics VII):
   (a) Safety Statistics Review dated November 20, 2013
   (b) Safety Statistics Review (Background Information for Advisory Committee) dated November 22, 2013

(4) Division of Pharmacovigilance I (DPV I) Review by Christian Cao dated May 20, 2014

(5) Division of Risk Management (DRISK) Risk Evaluation and Mitigation Strategy (REMS) Review by George Neyarapally dated May 7, 2014

(6) Clinical Pharmacology Reviews:
   (a) Clinical Pharmacology Review by Lanyan Fang, dated November 8, 2013

(b) Addendum to Clinical Pharmacology Review by Lanyan Fang, dated February 11, 2014

(7) Pharmacology/Toxicology Review by Tamal Chakraborti, dated November 20, 2013

(8) Microbiology Quality Reviews (Division of Good Manufacturing Practice Assessment):
   (a) Primary Microbiology Quality Review (Drug Product) by Steven Fong, dated November 26, 2013, and Addendum dated April 16, 2014
   (b) Primary Microbiology Quality Review (Drug Substance) by Reyes Candau-Chacon, dated December 12, 2013, and Addendum dated April 14, 2014

(9) Quality Reviews (Division of Monoclonal Antibodies):
   (a) Primary Quality Review by Qing Zhou, dated November 20, 2013, and Addendum dated February 20, 2014
   (b) Secondary Quality Review by Rashmi Rawat, dated November 27, 2013

(10) OSI Clinical Inspection Summary by Susan Leibenhaut, dated February 10, 2014

(11) Consult Reviews:
   (a) QT Interdisciplinary Review Team (QT-IRT) Consult Review by Qianyu Dang, dated October 1, 2013
   (b) Safety Consult Review (Liver Injury Cases) by Mark Avigan, dated January 29, 2014
   (c) Pediatric and Maternal Health Staff (PMHS) Consult Review (Pediatric Review) by Erica Wynn, dated January 29, 2014
   (d) Pediatric and Maternal Health Staff (PMHS) Consult Review (Maternal Health Review) by Carrie Ceresa, dated December 20, 2013

(12) Labeling Reviews:
   (a) Division of Medication Error Prevention and Analysis (DMEPA) Label, Labeling and Packaging Review by Lisa Khosla, dated November 26, 2013
   (b) DMEPA Proprietary Name Review by Lisa Khosla, dated August 19, 2013
   (c) Office of Professional Drug Promotion (OPDP) Review of Package Insert (PI) and Medication Guide (MG) by Adewale Adeleye, dated November 20, 2013
   (d) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Nathan Caulk, dated November 25, 2013
   (e) Division of Monoclonal Antibodies Carton and Container Review by Rashmi Rawat, dated November 20, 2013

The reviews should be consulted for more specific details of the current application.

3. CMC

The reader is referred to the Primary Quality Review by Qing Zhou, dated November 20, 2013, the Secondary Quality Review by Rashmi Rawat, dated November 27, 2013, and the Addendum to Primary Quality Review by Qing Zhou, dated February 20, 2014.

3.1 Overview

3.1.1 Overview of Drug Substance (DS)

The Quality Reviewers noted the following regarding the drug substance (DS):

- Vedolizumab DS is a recombinant, humanized, immunoglobulin IgG1, κ monoclonal antibody.
- It is directed to α4β7 integrin, which is expressed on T and B cells.

3.1.2 Overview of Drug Product (DP)

The Quality Reviewers noted the following regarding the drug product (DP):

- Vedolizumab DP is supplied as a sterile, lyophilized formulation for injection in a 20 mL single use vial.
- Each vial contains 300 mg (b) (4) of vedolizumab formulated in (b) (4) ((b) (4) L-histidine and (b) (4) L-histidine monohydrochloride), (b) (4) L-arginine hydrochloride, (b) (4) sucrose and (b) (4) polysorbate 80.
- Vedolizumab DP is reconstituted with 4.8 mL of sterile water for injection (USP) to yield a solution with an approximate pH of 6.3.
- The reconstitution time for lyophilized DP is ≤ 30 minutes.
- The lyophilized DP is a white to off white color cake, whereas the reconstituted DP solution is clear to opalascent, colorless to slightly yellow, and free of visible particulates.
- The recommended storage condition for vedolizumab DP is 2-8 °C, protected from light.
- The primary packaging components for vedolizumab drug product consist of a USP/Ph. Eur. Type 1, 20 ml clear (b) (4) glass vial that is sealed with a 20 mm, gray (b) (4) rubber stopper (b) (4)
- Vials are sealed with a 20 mm (b) (4) seal with a plastic cap.
- DP does not contain preservatives.
- DP vials are single-dose and should be discarded after use.
- The reconstituted vedolizumab DP is diluted into 250 mL of sterile 0.9% saline infusion bags prior to administration.
- The vedolizumab DP vial does not contain any overages.

3.2 Issues

3.2.1 Stability (DS and DP)

Overview - Stability of DS and DP: The Quality Reviewers noted the following regarding the stability of the DS and DP:

- The BLA submission contained adequate stability data to support establishment of a DS shelf life and a DP shelf life.
- Stability studies have been conducted in accordance with ICH Q1A(R2) and Q5C.
- DS and DP stability protocols, including specifications, conditions and testing intervals, were provided and found to be acceptable.

Stability of DS: The Quality Reviewers noted the following regarding the stability of DS:

- The data support a shelf life of (b) (4) months for the vedolizumab DS when stored at (b) (4) Although data are provided only through 30 months for the three registration batches at (b) (4), there are data for three additional representative DS batches demonstrating stability out to (b) (4) months when stored at (b) (4)
- The post-approval DS annual stability protocol testing includes pH, appearance, protein concentration, CEX-HPLC (charge profile), potency by binding assay and adhesion assay, SE-HPLC (% monomer and % aggregates), and reducing and non-reducing SDS-PAGE. Testing will be performed at 0, 6, 12, 24, 36 and 48 months.

Stability of DP: The Quality Reviewers noted the following regarding the stability of DP:

- The data support a shelf life of 36 months from the date of manufacture for vedolizumab (Entyvio) drug product when stored at 2-8 ^{o}C. The date of manufacture shall be defined as the (b) (4)
- The post-approval annual drug product stability protocol will store samples at 2-8 ^{o}C and testing will include color and clarity, appearance (cake), SEHPLC, CEX-HPLC, reducing and non-reducing SDS-PAGE, potency by binding assay and adhesion assay, moisture content, reconstitution time, pH, subvisible particles, endotoxin, sterility and CCI. Testing will be performed at 0, 6, 12, 24, and 36 and 48 months, with the exception of CCI and sterility testing. The CCI test will be performed at 12 and 24 months, and the sterility test will be performed at 0, 36, and 48 months.

DS and DP Release and Stability Specifications: The Quality Reviewers noted the following:

- DS and DP release and stability specifications based on clinical and manufacturing experience provided in the BLA are sufficient to ensure adequate quality and safety of vedolizumab for the initial marketed product.
- However, increased manufacturing experience gained post licensure can facilitate improved specifications.
- The current DS and DP release specifications include a *qualitative* non-reduced SDS-PAGE assay that does not provide control over the amounts of size-related impurities. The addition of a *quantitative* non-reduced SDS-based method will provide consistent

monitoring of the levels of low molecular weight size-related impurities in DS and DP throughout manufacture.
    - The sponsor has agreed to develop a non-reducing SDS-based assay that is capable of providing quantitative data for the evaluation of size-related impurities and to implement this assay in the release and stability programs for vedolizumab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria (see Section 13.6.4 - **Quality PMC #4**).
- The current DS release specifications include an ELISA method for evaluating host cell protein (HCP) levels in DS. This method detects various proteins from CHO cells, but this method is not optimal for the detection of proteins from the vedolizumab producing CHO cell line. The implementation of an improved, product-specific HCP assay will provide more accurate control of the host cell related impurities in DS.
    - The sponsor has agreed to develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential host cell proteins compared to the current assay and to implement this assay in the vedolizumab drug substance lot release program (see Section 13.6.4 - **Quality PMC #7**)..
- Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.
    - The sponsor has agreed to re-evaluate vedolizumab DS lot release and stability specifications after 30 lots have been manufactured at the commercial scale (see Section 13.6.4 - **Quality PMC #8**).
    - The sponsor has agreed to re-evaluate vedolizumab DP lot release and stability specifications after 30 lots have been manufactured at the commercial scale (see Section 13.6.4 - **Quality PMC #9**).

3.2.2 DS Manufacturing Process

Overview of DS Manufacturing Process: The Quality Reviewers noted the following regarding the DS manufacturing process:

- The DS manufacturing process was validated for consistency (b) (4)
- Concurrent validation protocols (b) (4) were included in the BLA and found to be acceptable.

Monoclonality of the Cell Line: The Quality Reviewers noted the following regarding the monoclonality of the cell line:

- Vedolizumab is produced using a CHO cell line that (b) (4)
- The (b) (4) cloning procedures used for the development of the production cell line do not provide sufficient assurance of the monoclonality of the cell line. The sponsor has agreed to provide supplemental data to support monoclonality (see Section 13.6.4 - **Quality PMC #1**).

- Until such data are provided, additional testing will be performed to assure that changes, such as the production and expansion of a new working cell bank, (b) (4)

DS Manufacturing Process Changes and Comparability: The Quality Reviewers noted the following regarding DS manufacturing process changes and comparability:

- The original process (Process A) used a murine cell line.
- Process B, which was used to produce the material used in Phase 1 and 2 clinical trials, used a CHO cell line for production.
- Materials generated using the two processes were found to be analytically comparable.
- The third process (Process C) was developed (b) (4) (b) (4)
- Process C material, also produced from the CHO cell line, was used in Phase 2 and 3 clinical trials, including the pivotal trials being evaluated under this BLA.
- Analytical comparability of Process B and Process C materials was established. Process C material was initially produced at a (b) (4) scale, and the scale was (b) (4) to (b) (4)
- The (b) (4) and (b) (4) Process C materials were shown to be analytically comparable. Process C at (b) (4) is the commercial manufacturing process.

3.2.3 DP Manufacturing Process

Overview of DP Manufacturing Process: The Quality Reviewers noted the following regarding the DP manufacturing process:

- The DP manufacturing process involves (b) (4)
- The DP manufacturing process was adequately validated.

Controls for Release of DP: The Quality Reviewers noted the following regarding the controls for release of DP:

- The controls for release of DP do not include testing for osmolality; the sponsor has agreed to develop and implement such testing as a PMC (see Section 13.6.4 - **Quality PMC #2**).
- The controls for release of DP do not include testing for polysorbate 80 levels; the sponsor has agreed to develop and implement such testing as a PMC (see Section 13.6.4 - **Quality PMC #3**).

3.2.4 Immunogenicity

The Quality Reviewers noted the following:

- The current assays are not sufficiently sensitive or drug tolerant to detect anti-drug antibody (ADA) in patients' samples.

- The sponsor was requested to provide a commitment to develop and validate sensitive detection and neutralization assays that can detect ADA in the presence of vedolizumab at levels that are expected to be present in the serum or plasma at the time of sampling (see Section 13.6.4 - **Quality PMC #5 and Quality PMC #6**).

3.2.5 Microbiology Quality Drug Substance

The Microbiology Quality Drug Substance Reviewer noted the following:

- Preliminary results do not show low endotoxin recovery (b) (4) Since the provisional results suggest no impact of formulated drug substance on endotoxin recovery, the risk for false endotoxin negatives in the finished product is deemed low.
    - The sponsor has agreed to conduct a maximum hold time study for the formulated drug substance using representative containers by July 2014. If low endotoxin recovery is found in the formulated drug substance during the maximum hold time study, either hold times will be reevaluated or an alternative method to measure endotoxin in formulated drug substance will be developed and validated by December 31, 2014 (see Section 13.6.5 - **Microbiology Quality Drug Substance PMC #1**).
- Preliminary results do not show low endotoxin recovery for the (b) (4) (b) (4) Since the provisional results suggest no impact of the on endotoxin recovery, the risk for false endotoxin negatives in the finished product is deemed low.
    - The sponsor has agreed to verify the endotoxin recovery results for the (b) (4) and establish action limits for this solution once the results are confirmed by a validated method. If low endotoxin recovery is found, maximum hold times (b) (4) will be established. The activities associated with this commitment will be completed and the final report will be submitted on or before 31 December 2014 (see Section 13.6.5 - **Microbiology Quality Drug Substance PMC #2**).

3.2.6 Microbiology Quality Drug Product

The Microbiology Quality Drug Product Reviewer noted the following:

- Microbiology Quality Stability Protocol: During stability testing, the container closure integrity test provides for a better assessment of maintenance of microbiology quality than the sterility test. The sponsor agreed to perform studies to determine the minimum leak size detectable by the dye and microbial ingress container closure integrity test methods (see Section 13.6.6 - **Microbiology Quality Drug Product PMC #1**).
- Bulk Drug Product Hold Periods: The proposed bulk drug product hold periods (b) (4) are acceptable based on:
  (1) The end of hold bioburden data for the commercial-scale lots used for validation. Acceptance criteria were (b) (4) and (b) (4) At all sampling points, the measured bioburden and endotoxin values were (b) (4) (b) (4) (b) (4).
  (2) The sponsor's agreement to conduct studies to update the hold periods once a validated endotoxin method becomes available (see Section 13.6.6 - **Microbiology Quality Drug Product PMC #2**).
- Endotoxin Acceptance Criterion for DP (b) (4) As noted in Section 3.2.3 of this CDTL Review above, the DP manufacturing process involves (b) (4) (b) (4) (b) (4) In response to the Agency's request, the Sponsor agreed to lower the DP (b) (4) acceptance criterion to ≤ (b) (4) and the DP (b) (4) criterion to (b) (4) In addition, the sponsor agreed to conduct controlled studies to validate an endotoxin assay for DP (b) (4) and to then implement routine endotoxin testing of the DP (b) (4) (see Section 13.6.6 - **Microbiology Quality Drug Product PMC #3**).

4. Nonclinical Pharmacology/Toxicology

4.1 Issues

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Tamal Chakraborti, dated November 20, 2013, for complete information.

The Nonclinical Reviewer noted that vedolizumab:

- is a selective integrin antagonist that binds to α4β7 integrin
- inhibited cellular adhesion interactions between α4β7 and MAdCAM-1 and fibronectin (an extracellular matrix glycoprotein)
- does not bind to α4β1 or αEβ7 integrin
- did not inhibit α4β7-VCAM-1, α4β1-VCAM-1, or α4β1-fibronectin-mediated adhesive interactions
- did not mediate antibody-dependent cell-mediated cytotoxicity (ADCC) and did not mediate complement dependent cytotoxicity (CDC) (a mechanism of cytotoxic action of many monoclonal antibodies)
- did not induce T lymphocyte activation or cytokine release in whole human blood

The Nonclinical Reviewer also noted the following key findings:

- The results of pharmacology studies appear to support the mechanism of action and the proposed indication of vedolizumab.
- In toxicology studies in monkeys, histopathological findings appeared to be due to the pharmacologic effect of vedolizumab (decreased trafficking of peripheral lymphocytes to the gut).
- The presence of Balantidium coli observed in the cecum and colon of monkeys did not appear to be treatment related.
- There was no apparent off-target toxicity in rabbits and monkeys following repeated administration. In addition, in tissue cross-reactivity studies with vedolizumab, no unanticipated tissue cross-reactivity or off-target staining was observed and results were consistent with the known pattern of α4β7 integrin expression.
- The potential of vedolizumab to cause PML was examined in an EAE model in the Rhesus monkey; an animal model of MS. Vedolizumab did not appear to inhibit immune surveillance of the CNS unlike natalizumab, which blocked immune surveillance of the CNS in this animal model. However, since EAE is not an animal model of PML; the results of this study do not directly demonstrate that MLN0002 has no potential to cause PML.

The Nonclinical Reviewer recommended that the sponsor conduct a juvenile animal toxicology study of 3 months duration in an appropriate species before initiation of the pediatric trial in patients 5 to 17 years of age (see Section 10 Pediatrics, and see Section 13.4 **- PREA PMR #2).**

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the BLA. The Nonclinical Reviewer additionally recommends that the proposed labeling be revised to include the following:

Section 8.1 of Label (Pregnancy)

Wording in the Pregnancy section should be revised to:

"**8.1 Pregnancy**

Pregnancy Category B

Risk Summary

There are no studies with Vedolizumab in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels (b) (4) times the recommended human dose. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if (b) (4)

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation day 7 (about (b) (4) times the recommended human dose based on body surface area) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre and postnatal development study in monkeys showed no evidence of any adverse effect on pre and postnatal development at intravenous doses up to 100 mg/kg (about (b) (4) times the recommended human dose (b) (4)

Section 8.3 of Label (Nursing Mothers)

"8.3 Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab is detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman."

Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility)

"13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of vedolizumab. Studies to evaluate the possible impairment of fertility or mutagenic potential of vedolizumab have not been performed."

(b) (4)

4.2 Recommendation

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the PREA PMR described above is agreed upon with the sponsor, and the labeling revisions described above are made.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology Review by Lanyan Fang, for complete information. The following is summarized from the Clinical Pharmacology Review.

5.1 Issues

5.1.1 Summary of Clinical Pharmacology Findings

The Clinical Pharmacology Reviewer noted that the pharmacokinetics (PK) and pharmacodynamic (PD) characteristics of vedolizumab in healthy subjects and subjects with UC or CD have been studied using the product manufactured with the commercial process (Process C) and clinical trial process (Process B). These two products have been demonstrated to be comparable.

Pharmacokinetics:

The Clinical Pharmacology Reviewer noted the following:

- Vedolizumab exhibits target-mediated drug disposition; hence, clearance decreases with increasing concentration due to target saturation at higher concentrations. The dose-normalized concentration-time profiles were similar for 300 and 600 mg after a single dose IV infusion, suggesting the saturation of the nonlinear clearance pathway at these doses and the linear clearance pathway is dominant. The serum half-life of vedolizumab was estimated to be approximately 18 to 21 days following 300 or 600 mg administration using non-compartmental analysis.
- No apparent differences were observed in vedolizumab PK in subjects with UC or CD based on the trough concentrations at Week 6 and at steady state during the maintenance phase. Additionally, the clearance of the linear pathway (CL_L) for subjects with UC and CD was estimated as 0.159 L/day and 0.155 L/day, respectively, based on a population PK analysis in which the Km and Vmax of the nonlinear elimination pathway were predefined to be the same value for subjects with UC and CD. The population PK analysis results showed no clinically meaningful impact on PK for the following covariates: severity of disease state, body weight, serum albumin, prior treatment with TNFα antagonist therapy, age (18-78 years) and co-administered medications.

Pharmacodynamics (PD, $\alpha_4\beta_7$ Receptor Occupancy):

The Clinical Pharmacology Reviewer noted the following:

- The relationship between vedolizumab serum concentration and the extent of α4β7 binding saturation was assessed based on data from MAdCAM-1-Fc biomarker (Study C13002). Maximum α4β7 binding saturation (i.e., ~ 100% inhibition of MAdCAM-1-Fc binding to α4β7) was achieved within one hour following the first vedolizumab dose at all dose levels ranging from 2 to 10 mg/kg in subjects with UC, i.e., the maximum α4β7 inhibition has no relationship with dose. The maximum inhibition remained throughout the whole treatment period until 84, 126 and 112 days after the last dose (at Day 85) for the 2, 6 and 10 mg/kg dose cohorts, respectively. Of note, the corresponding observed mean vedolizumab concentrations at the time of loss of near-maximal α4β7 inhibition were approximately 2 - 6 μg/mL.
- Given the proposed dosing regimen (300 mg Q8W, i.e., ~ 4 mg/kg Q8W), near-maximum α4β7 binding would be maintained during the entire dosing interval for the majority of subjects receiving the proposed 300 mg Q8W (mean trough ~10 μg/mL) dosing regimen.

Immunogenicity*:*

The Clinical Pharmacology Reviewer noted the following:

- The immunogenicity of vedolizumab during treatment could not be reliably assessed due to the drug interference issue in the immunogenicity assay. Specifically, the mean vedolizumab steady-state trough concentrations for the 300 mg Q8W and Q4W regimens were approximately 10 and 30 μg/mL, respectively. These levels were significantly greater than the drug tolerance level (i.e., 500 ng/mL) of the immunogenicity assay. Therefore, the incidence rate determined during the treatment phase is expected to be under-estimated.
- Based on data from Phase 3 Studies (C13006 and C13007), 56 of 1434 (4%) subjects who received continuous vedolizumab treatment in the maintenance phase (i.e., subjects who received VDZ in both induction and maintenance phase, VDZ/VDZ) developed anti-vedolizumab antibody (ADA) at any time during treatment. Nine of 56 subjects were persistently positive (positive ADA at two or more study visits) and 33 of 56 subjects developed neutralizing antibodies. Due to the aforementioned drug interference issue, the applicant-reported incidence rate of 4% is an underestimation.
- In subjects who received VDZ in the induction phase and placebo in the maintenance phase (VDZ/PBO), the immunogenicity incidence rate was 17% (20/117) at Week 52 when vedolizumab levels were undetectable and no drug interference issue was expected. However, since ADA could degrade during the long washout period, the incidence rate of 17% could still be an underestimation.
- ADA appeared to have affected the PK of vedolizumab. Six subjects with persistent ADA and available vedolizumab concentration data, all had a substantial decrease in their serum concentrations of vedolizumab, either to undetectable (N=5) or negligible levels (N=1) at Weeks 6 and 52.
- While the small number of ADA positive subjects precluded definitive conclusions regarding the impact of immunogenicity on the overall efficacy and safety in the phase 3 studies, none of the eight subjects with persistently positive ADA achieved clinical remission at Weeks 6 or 52.
- The sponsor agreed to conduct 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 (see Section 13.6.3 - **Clinical Pharmacology PMC #1**).

Disease-Drug-Drug Interactions (DDDI):

The Clinical Pharmacology Reviewer noted the following:

- The applicant did not assess the potential of vedolizumab to impact the PK of other coadministered drugs. As UC and CD involve chronic inflammation and are associated with an imbalanced cytokine network, indirect impacts on the formation of CYP450 enzymes cannot be ruled out. Therefore, the potential exists for an improvement in the inflammatory disease condition upon treatment with vedolizumab, to indirectly impact the expression of CYP450 enzymes. Thus, the applicant needs to evaluate the DDDI potential between vedolizumab and other CYP substrates which may be co-administered with vedolizumab, in the UC and CD population (see Section 13.6.3 - **Clinical Pharmacology PMC #2**).

Exposure-Response Relationship:

The Clinical Pharmacology Reviewer noted the following:

- UC: For the induction phase, a significant exposure-response relationship for clinical response and remission provides supportive evidence of effectiveness. Furthermore, exposure-response analyses indicate that a higher dose may provide additional benefit in the induction phase. However, considering the totality of evidence presented in the application for induction and maintenance phases, the proposed dose of 300 mg at week 0 and 2 in the induction phase appears reasonable for regulatory approval. We do recommend the sponsor explore the possibility of higher doses in the induction phase (post-approval) with the aim being to achieve higher remission rates. For the maintenance phase, no exposure-response was evident for clinical remission at Week 52. This was consistent with the lack of dose-response observed between the Q4W and Q8W dosing regimens. Thus, the applicant's proposal for the Q8W dosing regimen is acceptable.

- CD**:** Based on univariate and multivariate logistic regression analyses, no exposure-response was evident for the probability of clinical remission or enhanced clinical response as a function of mean trough concentrations. This was consistent with the lack of dose-response observed between the Q4W and Q8W dosing regimens at Week 52. Thus, the applicant's proposal for the Q8W dosing regimen is acceptable.

5.2 Recommendation

An Approval Action is the recommendation by the Clinical Pharmacology discipline.

6. Clinical Microbiology

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

7. Clinical/Statistical - Efficacy

The reader is referred to the Clinical Reviews by Laurie Muldowney (UC) and Klaus Gottlieb (CD), the Statistics Primary Reviews by Milton Fan (UC and CD), and the Statistics Secondary Review by Freda Cooner (UC and CD) for complete information.

7.1 Overview

7.1.1 Proposed Indications

The Applicant proposed the following ulcerative colitis (UC) and Crohn's disease (CD) indications:

- UC: "…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 a tumor necrosis factor-alpha (TNFα) antagonist."

- CD: "…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."

7.1.2 Overview of Phase 3 UC and CD Clinical Trials

An overview of the Phase 3 UC and CD clinical trials is shown in the table below.

Table 2. Phase 3 UC and CD Clinical Trials

Clinical Trials	Arms	Primary Endpoint	N*
UC			
C13006 Induction Trial	• PBO • VDZ 300 mg at Wks 0 and 2	• Clinical Response at Wk 6	374
C13006 Maintenance Trial[#]	• PBO • VDZ 300 mg Q4W (start at Wk 6) • VDZ 300 mg Q8W (start at Wk 6)	• Clinical Remission at Wk 52	373
CD			
C13007 Induction Trial	• PBO • VDZ 300 mg at Wks 0 and 2	• CDAI-100 Response at Wk 6[†] or • Clinical Remission at Wk 6[†]	368
C13007 Maintenance Trial[#]	• PBO • VDZ 300 mg Q4W (start at Wk 6) • VDZ 300 mg Q8W (start at Wk 6)	• Clinical Remission at Wk 52	461
C13011 Induction Trial	• PBO • VDZ 300 mg at Wks 0 and 2	• Clinical Remission at Wk 6[‡]	416

PBO: Placebo; VDZ: Vedolizumab; *ITT
[#] For each Maintenance Trial (C13006 and C13007), patients must have achieved Clinical Response at Wk 6 in the corresponding Induction Phase (see UC and CD Clinical Reviews for details)
[†]Alternative endpoints: at least one of the two alternative primary endpoints must be met to declare success (see CD Clinical Review for details)
[‡]Analysis population for the primary endpoint was the TNFα-antagonist-failure population (n=315)
UC: Clinical Response = Complete Mayo Score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
Clinical Remission = Complete Mayo Score of ≤ 2 points and no individual subscore > 1 point.
CD: CDAI-100 Response = Crohn's Disease Activity Index (CDAI) decrease from baseline by ≥100 points
Clinical Remission = CDAI ≤ 150 points
Table modified from UC and CD Clinical Reviews.

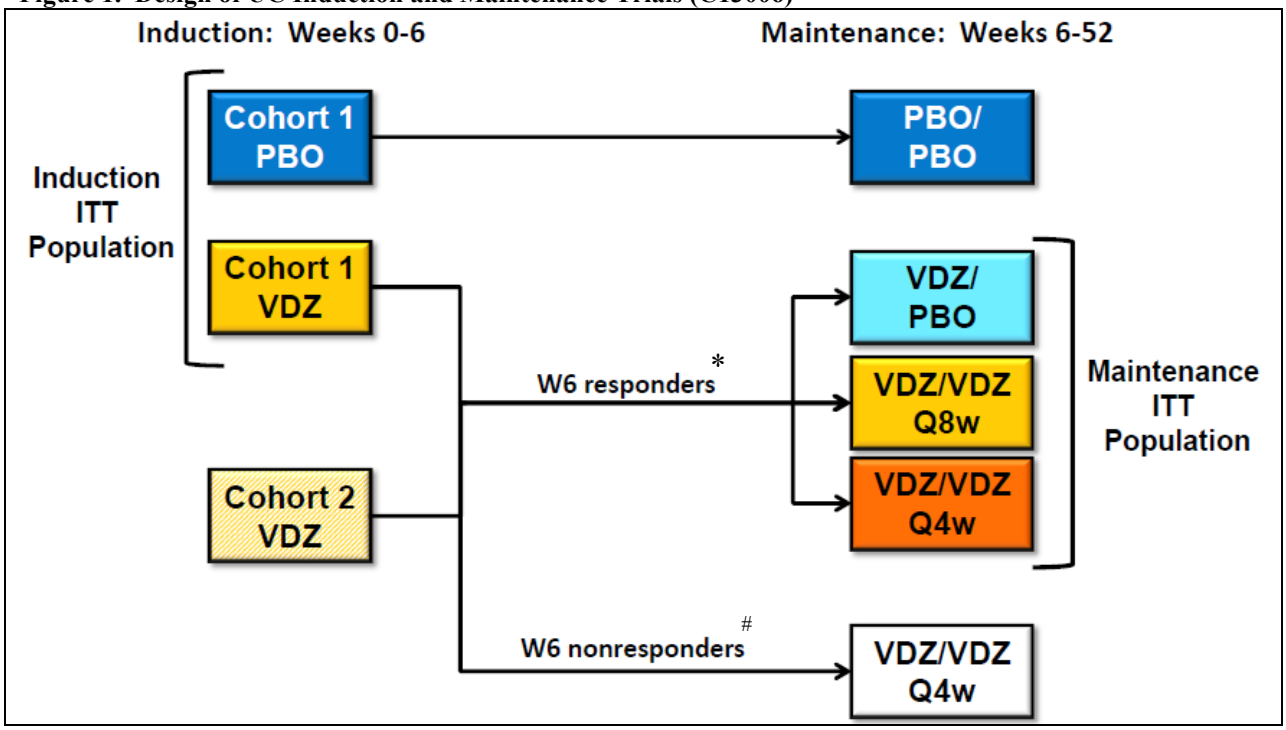
7.2 Design - UC Trials

7.2.1 C13006 (Induction and Maintenance)

Overview:

- The design of the UC induction and maintenance trials (C13006) is summarized in the figure below.

Figure 1. Design of UC Induction and Maintenance Trials (C13006)



The diagram above is taken from Slide 29 of the Applicant's December 9, 2013 Advisory Committee Meeting Presentation.

*Week 6 Responder/Non-responder status based on the following definition of clinical response: Clinical response: reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

Key Entry Criteria:

- Mayo Score: Moderately to severely active ulcerative colitis 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
- Prior Medications:
  - Enrolled patients in the United States (US) had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e., azathioprine or 6-mercaptopurine) and/or an inadequate response, loss of response, or intolerance to a TNFα-antagonist. (See Appendix 1 for specific entry criteria for inadequate response, loss of response, or intolerance to immunomodulators or TNFα-antagonists.)
  - Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five-year period the patients were corticosteroid dependent (i.e., unable to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response or intolerance to corticosteroids. (See Appendix 1 for specific entry criteria for corticosteroid dependence, inadequate response, or intolerance to corticosteroids.)
  - Patients that had received natalizumab ever in the past were excluded from enrollment.

- Patients that had received a TNFα-antagonist in the past 60 days were excluded from enrollment.

See additional details of entry criteria in the UC Clinical Review.

Randomization and Stratification:

- Induction Trial: Randomization into the induction trial was 3:2 (Cohort 1 VDZ:PBO) and stratified by:
  - concomitant use of oral corticosteroids; and
  - previous exposure to TNFα antagonists or concomitant immunomodulator (6-mercaptopurine or azathioprine) use.
- Cohort 2: After 375 patients were enrolled in the induction trial, approximately 451 additional patients were to be enrolled in Cohort 2.
- Maintenance Trial: Randomization into the maintenance trial was 1:1:1 (Placebo:VDZ Q8W:VDZ Q4W) and 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 (6-mercaptopurine or azathioprine)use.

Concomitant Immunomodulators:

- Enrolled patients in the US were required to discontinue concomitant immunomodulators (i.e., 6-mercaptopurine or azathioprine) by the end of the induction phase (i.e., Week 6).

Endpoints - Induction:

- The primary and secondary endpoints of the C13006 Induction Trial are shown in the table below.

Table 3. Primary and Secondary Endpoints of the C13006 Induction Trial

Endpoint	Definition
Primary	Clinical Response* at Week 6
1st Ranked Secondary	Clinical Remission# at Week 6
2nd Ranked Secondary	Mucosal Healing† at Week 6

*Clinical response: reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
#Clinical remission: complete Mayo score of ≤2 points and no individual subscore >1 point
†Mucosal Healing: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

Endpoints - Maintenance:

- The primary and secondary endpoints of the C13006 Maintenance Trial are shown in the table below.

Table 4. Primary and Secondary Endpoints of the C13006 Maintenance Trial

Endpoint	Definition
Primary	Clinical Remission at Week 52
1st Ranked Secondary	Durable Clinical Response*
2nd Ranked Secondary	Mucosal Healing at Week 52
3rd Ranked Secondary	Durable Clinical Remission[#]
4th Ranked Secondary	Corticosteroid-free Clinical Remission[†]

*Durable clinical response: Clinical response at both Weeks 6 and 52

[#]Durable clinical remission: Clinical remission at both Weeks 6 and 52

[†]Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at Week 6. Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.

7.3 Design - CD Trials

7.3.1 C13007 (Induction and Maintenance)

Overview:

- The design of the CD induction and maintenance trials (C13007) was the same as that for the UC induction and maintenance trials (C13006) shown in Figure 1 above. Note that Week 6 Responder/Nonresponder status was based on CDAI-70 Response (i.e., a ≥70-point decrease in CDAI score from baseline (Week 0)).

Key Entry Criteria:

- CDAI Score: 220 to 450[1]
- Prior Medications:
  - Enrolled patients in the United States (US) had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e., azathioprine, 6-mercaptopurine, or methotrexate) and/or an inadequate response, loss of response, or intolerance to one or more TNFα-antagonists. (See Appendix 1 for specific entry criteria for inadequate response, loss of response, or intolerance to immunomodulators or TNFα-antagonists.)
  - Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five-year period the patients were corticosteroid dependent (i.e., unable to successfully taper corticosteroids without a return of the symptoms of CD) or had an inadequate response or intolerance to corticosteroids. (See Appendix 1 for specific entry criteria for corticosteroid dependence, inadequate response, or intolerance to corticosteroids.)
  - Patients that had received natalizumab ever in the past were excluded from enrollment.

[1]Note that prior to Amendment 5/6 (July 6, 2009), the CDAI maximum for enrollment was 480. The percentage of patients that enrolled prior to Amendment 5/6 were by Cohort and Treatment Group: 32% (PBO Cohort 1), 31% (VDZ Cohort 1), and 0% (VDZ Cohort 2).

- Patients that had received a TNFα-antagonist in the past 60 days were excluded from enrollment.

See additional details of entry criteria in the CD Clinical Review.

Randomization and Stratification:

- Induction Trial: Randomization into the induction trial was 3:2 (Cohort 1 VDZ:PBO) and was to be stratified by:
  - concomitant use of oral corticosteroids; and
  - previous exposure to TNFα antagonists or concomitant immunomodulator (6-mercaptopurine, azathioprine, or methotrexate) use.
- Cohort 2: After 370 patients were enrolled in the induction trial, approximately 689 additional patients were to be enrolled in Cohort 2.
- Maintenance Trial: Randomization into the maintenance phase was 1:1:1 (Placebo:VDZ Q8W:VDZ Q4W) and was to be stratified by:
  - 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 (6-mercaptopurine, azathioprine, or methotrexate) use.

Concomitant Immunomodulators:

- Enrolled patients in the US were required to discontinue concomitant immunomodulators (i.e., 6-mercaptopurine, azathioprine, or methotrexate) by the end of the induction phase (i.e., Week 6).

Endpoints - Induction:

- The primary and secondary endpoints of the C13007 Induction Trial are shown in the table below.

Table 5. Primary and Secondary Endpoints of the C13007 Induction Trial

Endpoint	Definition
Primary *	Clinical Remission[#] at Week 6 or CDAI-100 Response[†] at Week 6
1st Ranked Secondary	Change in Serum CRP levels at Week 6

*Alternative Primary Endpoints: At least one of the two alternative primary endpoints must be met to declare success
[#]Clinical Remission: CDAI ≤ 150
[†]CDAI-100 Response: ≥ 100 decrease in CDAI from baseline (Week 0)

Endpoints - Maintenance:

- The primary and secondary endpoints of the C13007 Maintenance Trial are shown in the table below.

Table 6. Primary and Secondary Endpoints of the C13007 Maintenance Trial

Endpoint	Definition
Primary	Clinical Remission at Week 52
1st Ranked Secondary	CDAI-100 Response at Week 52
2nd Ranked Secondary	Corticosteroid-free Clinical Remission*
3rd Ranked Secondary	Durable Clinical Remission#

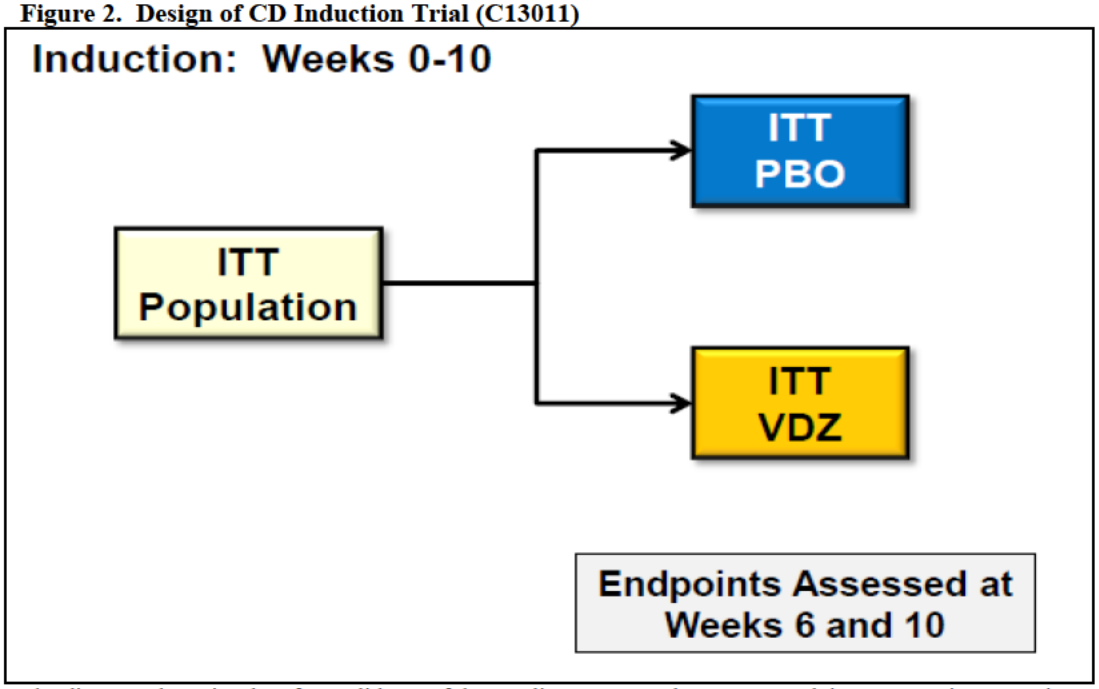
*Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in CDAI-70 response (≥70 decrease in CDAI from baseline) at Week 6. Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.
#Durable Clinical Remission: Clinical Remission in ≥80% of the study visits in the maintenance trial, including Week 52.

7.3.2 C13011 (Induction):

Overview:

- The design of the second CD induction trial (C13011) is shown in the figure below.

Figure 2. Design of CD Induction Trial (C13011)



The diagram above is taken from Slide 46 of the Applicant's December 9, 2013 Advisory Committee Meeting Presentation.

Key Entry Criteria:

- CDAI Score: 220 to 400
- Prior Medications: same as C13007 (see above)

See additional details of entry criteria in the CD Clinical Review.

Randomization and Stratification:

- Induction Trial: Randomization was 1:1 (PBO or VDZ) and was stratified by three factors:
  - Previous failure of TNFα antagonist therapy or naïve to TNFα antagonist therapy
  - Concomitant use of oral corticosteroids
  - Concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate)

Concomitant Immunomodulators:

- Enrolled patients in the US were required to discontinue concomitant immunomodulators (i.e., 6-mercaptopurine, azathioprine, or methotrexate) by the end of the induction phase (i.e., Week 10).

Endpoints - Induction:

- The primary and secondary endpoints of the C13011 Induction Trial are shown in the table below. The analysis population for the primary endpoint was the TNFα-antagonist-failure population. The analysis population for some secondary endpoints was the TNFα-antagonist-failure population; the analysis population for other secondary endpoints was the overall population.

Table 7. Primary and Secondary Endpoints of the C13011 Induction Trial

Endpoint	Definition	
	TNFα-antagonist-failure Population	Overall Population
Primary	Clinical Remission at Week 6	---
1st Ranked Secondary	---	Clinical Remission at Week 6
2nd Ranked Secondary	Clinical Remission at Week 10	---
3rd Ranked Secondary	---	Clinical Remission at Week 10
4th Ranked Secondary	Sustained Clinical Remission*	---
5th Ranked Secondary	---	Sustained Clinical Remission*
6th Ranked Secondary	CDAI-100 Response at Week 6	---

*Clinical Remission at both Weeks 6 and 10

7.4 Demographics and Baseline Characteristics - UC Trials

7.4.1 C13006 Induction:

Baseline Demographics

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 mean 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.

Baseline UC Disease Characteristics

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 (see table below).

Table 8. Comparison by Treatment Arm of Selected Baseline UC Disease Characteristics – Induction Study ITT Population (C13006)

Disease Characteristic	Placebo N = 149	VDZ N = 225
Duration of UC (years)[a] [Mean (std dev)]	7.1 (7.3)	6.1 (5.1)
Baseline disease activity[b] [Mean (std dev)]	8.6 (1.7)	8.5 (1.8)
Corticosteroid use at baseline or randomization, n (%)	84 (56%)	126 (56%)
Immunomodulator use at baseline or randomization n (%)	44 (30%)	75 (33%)
Prior TNFα use, n (%)	73 (49%)	95 (42%)
Prior TNFα failure, n (%)	63 (42%)	82 (36%)

Table above is modified from the Clinical Review by Laurie Muldowney
Source: Clinical Study Report C13006, Table 14, page 119
[a] Duration of ulcerative colitis is defined as (1 + first dose date – diagnosis date)/365.25
[b] Baseline disease activity represents the baseline complete Mayo score.

7.4.2 C13006 Maintenance:

Baseline Demographics

The baseline demographics in the maintenance phase were similar across treatment arms 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%). Fifty-five percent (55%) of patients were male and 82% were white. The mean age of study participants was 40.0 years old and the mean weight was approximately 75 kilograms.

Baseline UC Disease Characteristics

The baseline UC disease characteristics, including duration of disease, concomitant corticosteroid and/or immunomodulator use at baseline, and prior TNFα failure were similar across treatment arms (see table below).

Table 9. Comparison by Treatment Arm of Selected Baseline UC Disease Characteristics – Maintenance Study ITT Population (C13006)

Disease Characteristic	Placebo N = 126	VDZ Q8W N = 122	VDZ Q4W N=125
Duration of UC (years) [a] [Mean (std dev)]	7.8 (6.9)	6.2 (4.5)	7.6 (7.0)
Baseline disease activity [b] [Mean (std dev)]	8.4 (1.8)	8.4 (1.8)	8.3 (1.7)
Corticosteroid use at baseline or randomization, n (%)	72 (57%)	70 (57%)	73 (58%)
Immunomodulator use at baseline or randomization. n (%)	51 (40%)	43 (35%)	45 (36%)
Prior TNFα use, n (%)	47 (37%)	50 (41%)	52 (42%)
Prior TNFα failure, n (%)	38 (30%)	43 (35%)	40 (32%)

Table above is modified from the Clinical Review by Laurie Muldowney
Source: Clinical Study Report C13006, Table 49, page 194
[a] Duration of ulcerative colitis is defined as (1 + first dose date – diagnosis date)/365.25
[b] Baseline disease activity represents the baseline complete Mayo score.

7.5 Demographics and Baseline Characteristics - CD Trials

7.5.1 C13007 Induction

Baseline Demographics

The baseline demographics in the induction phase were similar across treatment arms and between Cohorts. Forty-seven percent (47%) of patients were male and 89% were white. The median age of study participants was 34.0 years old and the median weight was approximately 66 kilograms. About a third of overall patients were from North America with just under a quarter of overall patients from the US.

Baseline CD Disease Characteristics

The baseline CD disease characteristics, including duration of disease, concomitant corticosteroid and/or immunomodulator use at baseline, and prior TNFα failure were also similar across treatment arms (see table below).

Table 10. Comparison by Treatment Arm of Selected Baseline CD Disease Characteristics – Induction Study ITT Population (C13007)

Disease Characteristic	Placebo N = 148	VDZ N = 220
Duration of CD (years) [a] [Mean (std dev)]	8.2 (7.8)	9.2 (8.2)
Baseline disease activity [b] [Mean (std dev)]	325 (78)	327 (71)
Corticosteroid use at randomization, n (%)	71 (48%)	105 (48%)
Immunomodulator use at randomization. n (%)	51 (34%)	75 (34%)
Prior TNFα use, n (%)	72 (49%)	111 (50%)
Prior TNFα failure, n (%)	70 (47%)	105 (48%)

Source: Clinical Study Report C13007, Table 15, page 131
[a] Duration of Crohn's disease is defined as (1 + first dose date – diagnosis date)/365.25
[b] Baseline disease activity represents the baseline CDAI score.

7.5.2 C13007 Maintenance

Baseline Demographics

The baseline demographics in the maintenance phase were similar across treatment arms with the exception of 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). Forty-eight percent (48%) of patients were male and 89% were white. The mean age of study participants was 35.7 years old and the mean weight was approximately 70 kilograms.

Baseline CD Disease Characteristics

The baseline CD disease characteristics, including duration of disease, concomitant corticosteroid and/or immunomodulator use at baseline, and prior TNFα failure were also similar across treatment arms (see table below).

Table 11. Comparison by Treatment Arm of Selected Baseline CD Disease Characteristics – Maintenance Study ITT Population (C13007)

Disease Characteristic	Placebo N = 153	VDZ Q8W N = 154	VDZ Q4W N=154
Duration of CD (years) [a] [Mean (std dev)]	9.6 (8.9)	8.4 (7.3)	7.7 (6.8)
Baseline disease activity [b] [Mean (std dev)]	325 (66)	326 (69)	317 (66)
Corticosteroid use at randomization, n (%)	82 (54%)	88 (57%)	83 (54%)
Immunomodulator use at randomization, n (%)	49 (32%)	50 (32%)	53 (34%)
Prior TNFα use, n (%)	82 (54%)	82 (53%)	80 (52%)
Prior TNFα failure, n (%)	78 (51%)	82 (53%)	77 (50%)

Source: Clinical Study Report C13007, Table 53, page 221
[a] Duration of Crohn's disease is defined as (1 + first dose date – diagnosis date)/365.25
[b] Baseline disease activity represents the baseline CDAI score.

7.5.3 C13011 Induction

Baseline Demographics

The baseline demographics in the induction phase were similar across treatment arms. Forty-three percent (43%) of patients were male and 90% were white. The median age of study participants was 36.2 years old and the median weight was approximately 66 kilograms. About half of the patients were from North America.

Baseline CD Disease Characteristics

The baseline CD disease characteristics, including duration of disease and concomitant corticosteroid and/or immunomodulator use at baseline were also similar across treatment arms (see table below).

Table 12. Comparison by Treatment Arm of Selected Baseline CD Disease Characteristics – Induction Study TNFα Antagonist Failure ITT Population (C13011)

Disease Characteristic	Placebo N = 157	VDZ N = 158
Duration of CD (years)[a] [Mean (std dev)]	11.5 (8.1)	11.6 (8.6)
Baseline disease activity[b] [Mean (std dev)]	306 (55)	316 (53)
Corticosteroid use at baseline, n (%)	85 (54%)	86 (54%)
Immunomodulator use at randomization, n (%)	42 (27%)	43 (27%)

Source: Clinical Study Report C13011, Table 10-10, pages 93-94
[a]Duration of Crohn's disease is defined as (1 + first dose date – diagnosis date)/365.25
[b]Baseline disease activity represents the baseline CDAI score.

7.6 Disposition - UC Trials

7.6.1 C13006 Induction:

Twenty-one (21) patients (14 in the placebo group and seven in the VDZ Cohort 1 group) 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.

The UC Clinical Reviewer noted that the number of early discontinuations from the Induction Study was small and would not be expected to impact the results (see UC Clinical Review).

7.6.2 C13006 Maintenance:

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 true AEs.

The UC Clinical Reviewer noted that although there were a large number of discontinuations in the Maintenance Phase with a higher number of discontinuations from the placebo arm, 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 that show internal consistency (see UC Clinical Review).

7.7 Disposition - CD Trials

7.7.1 C13007 Induction

Thirty-two (32) patients (seven in the placebo group and nine in the VDZ Cohort 1 group) discontinued from the Induction Study prior to completion, and the primary reasons for discontinuation were AEs, withdrawal of consent, and lack of efficacy. An additional 73 patients from Cohort 2 discontinued prior to completion of the Induction Phase.

The number of discontinuations was small and would not be expected to impact the results (see CD Clinical Review).

7.7.2 C13007 Maintenance

There were 242 patients (52%) who discontinued from the Maintenance Study prior to completion, and the majority of these patients were from the placebo arm (89 patients, 58%). The primary reason for discontinuation was lack of efficacy, and more patients discontinued due to lack of efficacy from the placebo arm (64 patients, 42%) than from either vedolizumab arm (58 patients, 38% and 48 patients, 31% 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 true AEs.

7.7.3 C13011 Induction

Nineteen (19) patients (12 in the placebo group and seven in the VDZ group) discontinued from the Induction Study prior to completion, and the primary reasons for discontinuation were AEs and lack of efficacy.

The number of early discontinuations from the Induction Study was small and would not be expected to impact the results (see CD Clinical Review).

7.8 UC Trials - Efficacy Results

7.8.1 C13006 Induction

Overall Results - Induction

The results of the UC Phase 3 induction trial are shown in the table below.

Table 13. UC Induction (C13006)

Endpoint		PBO N=149	VDZ N=225	p	Δ	95% CI
1^0	Clinical Response at Wk 6	25.5%	47.1%	< 0.0001	**21.7%**	11.6%, 31.7%
1st 2^0	Clinical Remission at Wk 6	5.4%	16.9%	0.0009	**11.5%**	4.7%, 18.3%
2nd 2^0	Mucosal Healing at Wk 6*	24.8%	40.9%	0.0012	**16.1%**	6.4%, 25.9%

* Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Pages 122, 127, and 131 of the C13006 Study Report

The single UC induction trial (C13006 Induction) demonstrated superiority of vedolizumab over placebo for Clinical Response at Week 6. In addition, both of the pre-specified secondary endpoints (Clinical Remission at Week 6 and "Mucosal Healing"[2] at Week 6) were met. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data (see Section 12.3 of this CDTL Review).

[2] Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.

Key Subgroup and Other Analyses - Induction

TNFα-Antagonist (Inadequate Response, Loss of Response, or Intolerance vs. No Prior Use): The treatment difference for each of the three endpoints (primary endpoint of clinical response at Week 6 and the two secondary endpoints of clinical remission at Week 6 and mucosal healing[3] at Week 6) was numerically lower in the subgroup of patients that had an inadequate response, loss of response, or intolerance to a TNFα antagonist than in the subgroup of patients that had no prior use of a TNFα antagonist. See table below.

Table 14. Subgroup Analysis - Inadequate Response, Loss of Response, or Intolerance to a TNFα Antagonist vs. No Prior Use of a TNFα Antagonist (C13006 Induction)

Endpoint	TNFα Antagonist					
	Inadequate Response, Loss of Response, or Intolerance			No Prior Use		
	PBO N=63	VDZ N=82	Δ	PBO N=76	VDZ N=130	Δ
Clinical Response at Week 6	20.6%	39.0%	**18.4%**	26.3%	53.1%	**26.8%**
Clinical Remission at Week 6	3.2%	9.8%	**6.6%**	6.6%	23.1%	**16.5%**
Mucosal Healing at Week 6*	20.6%	30.5%	**9.9%**	25.0%	49.2%	**24.2%**

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Page 134 of the C13006 Study Report

US Protocol Criteria: The treatment difference for each of the three endpoints (primary endpoint of clinical response at Week 6 and the two secondary endpoints of clinical remission at Week 6 and mucosal healing[3] at Week 6) was numerically lower in the subgroup of patients that met US Protocol Criteria[4] than in the subgroup of patients that did not meet US Protocol Criteria. See table below.

Table 15. Subgroup Analysis - Met US Protocol Criteria (Yes vs. No) (C13006 Induction)

Endpoint	Met US Protocol Criteria					
	Yes			No		
	PBO N=85	VDZ N=112	Δ	PBO N=64	VDZ N=113	Δ
Clinical Response at Week 6	23.5%	37.5%	**14.0%**	28.1%	56.6%	**28.5%**
Clinical Remission at Week 6	5.9%	10.7%	**4.8%**	4.7%	23.0%	**18.3%**
Mucosal Healing at Week 6*	24.7%	30.4%	**5.7%**	25.0%	51.3%	**26.3%**

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Pages 25, 26, and 27 of the Response to IR received August 26, 2013

[3]Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
[4] US protocol criteria required patients to have failed either an immunomodulator (5-mercaptopurine or azathioprine) or a TNFα antagonist, while outside the US failing corticosteroids was sufficient for study entry. In addition, US protocol criteria status required patients to discontinue immunomodulators by Week 6. (See Section 7.1.3 of this CDTL Review.)

Baseline Concomitant Immunomodulator Use: The treatment difference for the primary endpoint of clinical response at Week 6 appeared to be similar in the subgroup of patients with baseline concomitant immunomodulator use and the subgroup of patients without baseline concomitant immunomodulator use. The treatment difference for each of the secondary endpoints of clinical remission at Week 6 and mucosal healing[3] at Week 6 was numerically higher in the subgroup of patients with baseline concomitant immunomodulator use than in the subgroup of patients without baseline concomitant immunomodulator use. See table below.

Table 16. Subgroup Analysis - Baseline Concomitant Immunomodulator Use (Yes vs. No) (C13006 Induction)

Endpoint	Baseline Concomitant Immunomodulator Use					
	Yes			No		
	PBO N=44	VDZ N=75	Δ	PBO N=105	VDZ N=150	Δ
Clinical Response at Week 6	34.1%	53.3%	**19.2%**	21.9%	44.0%	**22.1%**
Clinical Remission at Week 6	6.8%	26.7%	**19.8%**	4.8%	12.0%	**7.2%**
Mucosal Healing at Week 6*	27.3%	48.0%	**20.7%**	23.8%	37.3%	**13.5%**

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Page 137 of the C13006 Study Report

Demographic and Baseline Characteristics: The Clinical Reviewer noted that the results were consistent across age, gender, race, geographic region, duration of disease, and baseline disease activity (see UC Clinical Review).

The UC Clinical Reviewer noted that the above subgroup analyses should be interpreted with caution because they were post hoc and were based on small sample sizes. The Secondary Statistics Reviewer noted that that the subgroup analyses showed an expected variability of the treatment effect and should be viewed with caution due to their exploratory nature. The Secondary Statistics Reviewed also noted that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

Other Analyses - Induction

Exploratory Analysis using a Different (More Stringent) Definition of Clinical Remission: The Primary Statistics Reviewer conducted an exploratory analysis using a different (more stringent) definition of clinical remission than that pre-specified in the protocol; the definition was Endoscopy subscore = 0; Rectal Bleeding subscore = 0; and Stool Frequency decrease or no change (see UC Primary Statistics Review). Although statistical insignificance was concluded in the Primary Statistics Review based on this definition, the Secondary Statistics Reviewer noted that such a result might be expected because the study was not designed or powered to show statistical significance on this endpoint.

Sensitivity Analyses Using Different Imputation Methods on the Missing Data: The Secondary Statistics Reviewer noted that extensive sensitivity analyses using different imputation methods on the missing data were requested by the Agency and conducted by the Applicant. The Secondary Statistics Reviewed also noted that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

7.8.2 C13006 Maintenance:

Overall Results - Maintenance

The results of the UC Phase 3 maintenance trial are shown in the table below.

Table 17. UC Maintenance (C13006)

Endpoint		PBO	VDZ Q8W	VDZ Q4W	VDZ Q8W - PBO			VDZ Q4W - PBO		
					p	Δ	95% CI	p	Δ	95% CI
1^0	Clinical Remission at Wk 52	15.9% (20/126)	41.8% (51/122)	44.8% (56/125)	< 0.0001	**26.1%**	14.9%, 37.2%	< 0.0001	**29.1%**	17.9%, 40.4%
1st 2^0	Durable Clinical Response	23.8% (30/126)	56.6% (69/122)	52.0% (65/125)	< 0.0001	**32.8%**	20.8%, 44.7%	< 0.0001	**28.5%**	16.7%, 40.3%
2nd 2^0	Mucosal Healing at Wk 52*	19.8% (25/126)	51.6% (63/122)	56.0% (70/125)	< 0.0001	**32.0%**	20.3%, 43.8%	< 0.0001	**36.3%**	24.4%, 48.3%
3rd 2^0	Durable Clinical Remission	8.7% (11/126)	20.5% (25/122)	24.0% (30/125)	0.0079	**11.8%**	3.1%, 20.5%	0.0009	**15.3%**	6.2%, 24.4%
4th 2^0	Corticosteroid -free Remission at Wk 52	13.9% (10/72)	31.4% (22/70)	45.2% (33/73)	0.0120	**17.6%**	3.9%, 31.3%	< 0.0001	**31.4%**	16.6%, 46.2%

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Pages 198, 204, 205, 206, and 207 of the C13006 Study Report

The single UC maintenance trial (C13006 Maintenance) demonstrated superiority of both vedolizumab arms over placebo for Clinical Remission at Week 52. In addition, all four of the pre-specified secondary endpoints (Durable Clinical Response[5], "Mucosal Healing"[2], Durable Clinical Remission[6], and Corticosteroid-Free Remission[7]) were met. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data (see Section 12.3 of this CDTL Review).

The UC Clinical Reviewer recommended that after the initial doses at Weeks 0, 2, and 6, the Q8W dosing regimen be the recommended dosing regimen because there was no difference in efficacy appreciated between the Q8W and Q4W dosing regimens. (See Section 12.3 of this CDTL Review.)

[5] Durable Clinical Response was defined as Clinical Response both at Week 6 and Week 52
[6] Durable Clinical Remission was defined as Clinical Remission both at Week 6 and Week 52
[7] Corticosteroid-Free Remission was defined as Clinical remission in patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.

Key Subgroup Analyses - Maintenance

The subgroup analyses below show results for the Q8W arm and placebo. The Q8W dosing regimen is the recommended dosing regimen.

TNFα Antagonist (Inadequate Response, Loss of Response, or Intolerance vs. No Prior Use): The treatment differences for the primary endpoint of clinical remission at Week 52 and for the third secondary endpoint of durable clinical remission were numerically higher in the subgroup of patients with an inadequate response, loss of response, or intolerance to a TNFα-antagonist than in the subgroup of patients with no prior use of a TNFα-antagonist. The treatment difference for the first secondary endpoint of durable clinical response was numerically lower in the subgroup of patients with an inadequate response, loss of response, or intolerance to a TNFα-antagonist than in the subgroup of patients with no prior use of a TNFα-antagonist. The treatment differences for the second secondary endpoint of mucosal healing[3] at Week 52 and the fourth secondary endpoint of corticosteroid-free remission at Week 52 appeared to be similar in both subgroups. See table below.

Table 18. Subgroup Analysis - Inadequate Response, Loss of Response, or Intolerance to a TNFα-Antagonist vs. No Prior Use of a TNFα Antagonist (C13006 Maintenance)

Endpoint	TNFα-Antagonist					
	Inadequate Response, Loss of Response, or Intolerance			No Prior Use		
	PBO	VDZ Q8W	Δ	PBO	VDZ Q8W	Δ
Clinical Remission at Wk 52	5.3% (2/38)	37.2% (16/43)	**31.9%**	19.0% (15/79)	45.8% (33/72)	**26.8%**
Durable Clinical Response	15.8% (6/38)	46.5% (20/43)	**30.7%**	26.6% (21/79)	65.3% (47/72)	**38.7%**
Mucosal Healing at Wk 52*	7.9% (3/38)	41.9% (18/43)	**34.0%**	24.1% (19/79)	59.7% (43/72)	**35.7%**
Durable Clinical Remission	2.6% (1/38)	20.9% (9/43)	**18.3%**	12.7% (10/79)	22.2% (16/72)	**9.6%**
Corticosteroid-free Remission at Wk 52	4.3% (1/23)	23.1% (6/26)	**18.7%**	18.6% (8/43)	35.9% (14/39)	**17.3%**

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Page 210 of the C13006 Study Report

US Protocol Criteria: The treatment differences for the primary endpoint of clinical remission at Week 52, the third secondary endpoint of durable clinical remission, and the fourth secondary endpoint of corticosteroid-free remission at Week 52 were numerically higher in the subgroup of patients that met US Protocol Criteria[4] than in the subgroup of patients that did not meet US Protocol Criteria. The treatment difference for the first secondary endpoint of durable clinical response was numerically lower in the subgroup of patients that met US Protocol Criteria than in the subgroup of patients that did not meet US Protocol Criteria. The treatment difference for the second secondary endpoint of mucosal healing[3] at Week 52 appeared to be similar in both subgroups. See table below.

Table 19. Subgroup Analysis - Met US Protocol Criteria (Yes vs. No) (C13006 Maintenance)

Endpoint	Met US Protocol Criteria					
	Yes			No		
	PBO	VDZ Q8W	Δ	PBO	VDZ Q8W	Δ
Clinical Remission at Wk 52	5.6% (3/54)	35.6% (21/59)	**30.0%**	23.6% (17/72)	47.6% (30/63)	**24.0%**
Durable Clinical Response	14.8% (8/54)	45.8% (27/59)	**30.9%**	30.6% (22/72)	66.7% (42/63)	**36.1%**
Mucosal Healing at Wk 52*	11.1% (6/54)	42.4% (25/59)	**31.3%**	26.4% (19/72)	60.3% (38/63)	**33.9%**
Durable Clinical Remission	3.7% (2/54)	18.6% (11/59)	**14.9%**	12.5% (9/72)	22.2% (14/63)	**9.7%**
Corticosteroid-free Remission at Wk 52	5.9% (2/34)	25.7% (9/35)	**19.8%**	21.1% (8/38)	37.1% (13/35)	**16.1%**

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Pages 28, 29, 30, 31, and 32 of the Response to IR received August 26, 2013

Baseline Concomitant Immunomodulator Use: The treatment differences for the primary endpoint of clinical remission at Week 52, the second secondary endpoint of mucosal healing[3] at Week 52, and the fourth secondary endpoint of corticosteroid-free remission at Week 52 appeared to be similar in the subgroup with baseline concomitant immunomodulator use and the subgroup without baseline concomitant immunomodulator use. The treatment difference for the first secondary endpoint of durable clinical response was numerically higher in the subgroup with baseline concomitant immunomodulator use than in the subgroup without baseline concomitant immunomodulator use. The treatment difference for the third secondary endpoint of durable clinical remission was numerically higher in the subgroup without baseline concomitant immunomodulator use than in the subgroup with baseline concomitant immunomodulator use. See table below.

Table 20. Subgroup Analysis - Baseline Concomitant Immunomodulator Use (Yes vs. No) (C13006 Maintenance)

Endpoint	Baseline Concomitant Immunomodulator Use					
	Yes			No		
	PBO	VDZ Q8W	Δ	PBO	VDZ Q8W	Δ
Clinical Remission at Wk 52	19.6% (10/51)	44.2% (19/43)	**24.6%**	13.3% (10/75)	40.5% (32/79)	**27.2%**
Durable Clinical Response	27.5% (14/51)	67.4% (29/43)	**40.0%**	21.3% (16/75)	50.6% (40/79)	**29.3%**
Mucosal Healing at Wk 52*	23.5% (12/51)	53.5% (23/43)	**30.0%**	17.3% (13/75)	50.6% (40/79)	**33.3%**
Durable Clinical Remission	13.7% (7/51)	23.3% (10/43)	**9.5%**	5.3% (4/75)	19.0% (15/79)	**13.7%**
Corticosteroid-free Remission at Wk 52	16.7% (4/24)	31.8% (7/22)	**15.2%**	12.5% (6/48)	31.3% (15/48)	**18.8%**

*Mucosal Healing was defined as a Mayo endoscopic subscore of ≤ 1 point. Note that a "mucosal healing" labeling claim would require histologic data, and the applicant provided no histologic data.
Source: Pages 214-215 of the C13006 Study Report

Demographic and Baseline Characteristics: The Clinical Reviewer noted that the results were consistent across age, gender, race, geographic region, duration of disease, and baseline disease activity (see UC Clinical Review).

The UC Clinical Reviewer noted that the above subgroup analyses should be interpreted with caution because they were post hoc and were based on small sample sizes. The Secondary Statistics Reviewer noted that that the subgroup analyses showed an expected variability of the treatment effect and should be viewed with caution due to their exploratory nature. The Secondary Statistics Reviewer also noted that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

Other Analyses - Maintenance

Sensitivity Analyses Using Different Imputation Methods on the Missing Data: The Secondary Statistics Reviewer noted that extensive sensitivity analyses using different imputation methods on the missing data were requested by the Agency and conducted by the Applicant, and that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

7.9 CD Trials - Efficacy Results

7.9.1 Induction:

Overall Results - Induction

The results of the CD Phase 3 induction trials are shown in the tables below.

Table 21. CD Induction (C13007)

Endpoint		PBO	VDZ	p	Δ	95% CI
1^0	Clinical Remission at Wk 6	6.8% (10/148)	14.5% (32/220)	0.0206	**7.8%**	1.2, 14.3
1st 2^0	Change in CRP (Mean, SD)	19.9 (30.0)	21.1 (26.9)	0.9288	**0.2**	--

Source: Pages 136 and 140 of the C13007 Study Report

Table 22. CD Induction (C13011)

Endpoint		PBO	VDZ	p	Δ	95% CI
1^0	Clinical Remission at Wk 6	12.1% (19/157)	15.2% (24/158)	0.4332	**3.0%**	-4.5, 10.5

Source: Page 100 of the C13011 Study Report

Of the two CD induction trials (C13007 and C13011), only one (C13007) showed superiority of vedolizumab over placebo for induction of clinical remission. Neither the pre-specified alternative primary endpoint nor the pre-specified secondary endpoint was met.

We questioned whether the level of evidence requirements for a single trial were met to establish substantial evidence of efficacy for induction of clinical remission in CD based on

the Evidence of Effectiveness Guidance.[8] The Guidance states, in general terms, that a single trial would be acceptable for approval of an indication if it provided strength of evidence equal to two adequate and well-controlled trials. Key considerations (also described in the Guidance) include: (1) whether the observed outcome of the C13007 induction trial was statistically very persuasive; and (2) whether multiple prospectively identified endpoints involving different events (each of which represents a beneficial, but different, effect) were met.

Study C13011 did not meet its primary endpoint. The Clinical Reviewer noted that exploratory analyses in the overall study population (i.e., not limited to TNFα Antagonist Failures) at Week 6 suggested that there may be a treatment effect in the overall study population. Additionally, since a third dose at Week 6 was administered, the Clinical Reviewer noted that exploratory efficacy analyses at a later timepoint (Week 10) (in both the overall and the TNFα Antagonist Failures study populations) suggested that there may be a treatment effect at the later timepoint. However, these exploratory analyses need to be interpreted with caution. (See the CD Clinical Review by Klaus Gottlieb.)

The majority of the Advisory Committee members (12 versus 9) voted that the data support the efficacy of vedolizumab for the proposed CD induction indication (see Section 9 of this CDTL Review).

The CD Clinical Reviewer concluded that efficacy was demonstrated in CD but recommended the term "achieving" over "inducing and maintaining" clinical response and remission for the indication (see Sections 7.9.2 and 12.3 of this CDTL Review; see also the CD Clinical Review by Klaus Gottlieb).

Key Subgroup Analyses - Induction

The subgroup analyses below are for Study C13007. Subgroup analyses for Study C13011 are not shown as the study did not meet its primary endpoint.

TNFα-Antagonist (Inadequate Response, Loss of Response, or Intolerance vs. No Prior Use): The treatment difference for clinical remission at Week 6 was numerically lower in the subgroup with inadequate response, loss of response, or intolerance to a TNFα-antagonist than in the subgroup with no prior use of a TNFα-antagonist. See table below.

Table 23. Subgroup Analysis - Inadequate Response, Loss of Response, or Intolerance to a TNFα-Antagonist vs. No Prior Use of a TNFα Antagonist (C13007 Induction)

Endpoint	TNFα-Antagonist					
	Inadequate Response, Loss of Response, or Intolerance			No Prior Use		
	PBO N=70	VDZ N=105	Δ	PBO N=76	VDZ N=109	Δ
Clinical Remission at Wk 6	4.3%	10.5%	**6.2%**	9.2%	17.4%	**8.2%**

Source: Page 141 of the C13007 Study Report

[8] FDA Guidance "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" (available at http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf)

US Protocol Criteria: The treatment difference for clinical remission at Week 6 was numerically lower in the subgroup that met US Protocol Criteria[4] than in the subgroup that did not meet US Protocol Criteria. See table below.

Table 24. Subgroup Analysis - Met US Protocol Criteria (Yes vs. No) (C13007 Induction)

Endpoint	Met US Protocol Criteria					
	Yes			No		
	PBO N=75	VDZ N=120	Δ	PBO N=73	VDZ N=100	Δ
Clinical Remission at Wk 6	5.3%	11.7%	**6.3%**	8.2%	18.0%	**9.8%**

Source: Page 33 of the Response to IR received August 26, 2013

Baseline Concomitant Immunomodulator Use: The treatment difference for clinical remission at Week 6 was numerically lower in the subgroup with baseline concomitant immunomodulator use than in the subgroup without baseline concomitant immunomodulator use. See table below.

Table 25. Subgroup Analysis - Baseline Concomitant Immunomodulator Use (Yes vs. No) (C13007 Induction)

Endpoint	Baseline Concomitant Immunomodulator Use					
	Yes			No		
	PBO N=51	VDZ N=75	Δ	PBO N=97	VDZ N=145	Δ
Clinical Remission at Wk 6	7.8%	13.3%	**5.5%**	6.2%	15.2%	**9.0%**

Source: Page 146 of the C13007 Study Report

Demographic and Baseline Characteristics: The Clinical Reviewer noted that the results were consistent across age, gender, race, geographic region, duration of disease, and baseline disease activity (see CD Clinical Review).

The CD Clinical Reviewer noted that the above subgroup analyses should be interpreted with caution because they were post hoc and were based on small sample sizes. The Secondary Statistics Reviewer noted that that the subgroup analyses showed an expected variability of the treatment effect and should be viewed with caution due to their exploratory nature. The Secondary Statistics Reviewer also noted that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

Other Analyses - Induction

Exploratory Analyses on Patients with Baseline CDAI Score Lower than the Pre-specified Lower Limit of 220 using the Fisher's Exact Test: The Primary Statistics Reviewer conducted several exploratory analyses on patients with baseline CDAI score lower than the pre-specified lower limit of 220. The Secondary Statistics Reviewer noted that the screening CDAI score (rather than the baseline CDAI score) should be used for these analyses because the screening records were used for eligibility determination; and that using these data there were 8 patients evenly distributed between the two treatment groups who had protocol violations by having a screening CDAI score less than 220 (instead of the 20 patients identified in the Primary Statistics Review). The Secondary Statistics Reviewer also noted

that the Primary Statistics Reviewer applied the Fisher's exact test (instead of the pre-specified Cochran-Mantel-Haenszel (CMH) test) for these exploratory analyses, and that with the relatively small treatment effect size, and the discrete nature of the data, the sensitivity of the p-value to a few patients' data or to the use of an exact test of proportions is not an unexpected result nor one that should necessarily have been a significant review issue. The Secondary Statistics Reviewer concluded that the assumptions underlying the Applicant's use of the CMH test statistic for Study C13007 are defensible, and the proper p-value for the primary comparison should be based on that analysis with the pre-specified primary analysis population. Thus, the Secondary Statistics Reviewer concluded that the statistical insignificance stated in the primary review should be viewed with caution due to the exploratory nature of these exploratory analyses.

Sensitivity Analyses Using Different Imputation Methods on the Missing Data: The Secondary Statistics Reviewer noted that extensive sensitivity analyses using different imputation methods on the missing data were requested by the Agency and conducted by the Applicant, and that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

7.9.2 Maintenance:

Overall Results - Maintenance

The results of the CD Phase 3 maintenance trial are shown in the table below.

Table 26. CD Maintenance (C13007)

Endpoint		PBO	VDZ Q8W	VDZ Q4W	VDZ Q8W - PBO			VDZ Q4W - PBO		
					p	Δ	95% CI	p	Δ	95% CI
1^0	Clinical Remission at Wk 52	21.6% (33/153)	39.0% (60/154)	36.4% (56/154)	0.0007	**17.4%**	7.3, 27.5	0.0042	**14.7%**	4.6, 24.7
1st 2^0	CDAI-100 Response at Wk 52	30.1% (46/153)	43.5% (67/154)	45.5% (70/154)	0.0132	**13.4%**	2.8, 24.0	0.0053	**15.3%**	4.6, 26.0
2nd 2^0	Corticosteroid-free Remission at Wk 52	15.9% (13/82)	31.7% (26/82)	28.8% (23/80)	0.0154	**15.9%**	3.0, 28.7	0.0450	**12.9%**	0.3, 25.5
3rd 2^0	Durable Clinical Remission*	14.4% (22/153)	21.4% (33/154)	16.2% (25/154)	0.1036	**7.2%**	-1.5, 16.0	0.6413	**2.0%**	-6.3, 10.2

*Durable Clinical Remission was defined as Clinical Remission at ≥80% of study visits including final visit (Week 52)
Source: Pages 229, 238, 246, and 248 of the C13007 Study Report

The single maintenance trial (C13007 Maintenance) demonstrated superiority of both vedolizumab arms over placebo for Clinical Remission at Week 52. In addition, two of the three pre-specified secondary endpoints were met (CDAI-100 Response, Corticosteroid-free Remission) for both the Q4W and Q8W arms. It should be noted that the secondary endpoint of Durable Clinical Remission was not met for either the Q4W or Q8W arms.

We questioned if substantial evidence of efficacy for maintenance of clinical remission can be demonstrated without first having demonstrated substantial evidence of efficacy for induction of clinical remission. The efficacy standard that has been used in prior drug approvals (consistent with the Evidence of Effectiveness Guidance) is that if there is substantial evidence of efficacy for induction (in a disease population; e.g., UC or CD), a single successful maintenance trial (in that same disease population) could be sufficient to extend the claim to maintenance (see Section 2.5.2 of this CDTL Review).

Twenty Advisory Committee members (with one abstaining) voted that the data support the efficacy of vedolizumab for the proposed CD maintenance indication (see Section 9 of this CDTL Review).

The CD Clinical Reviewer concluded that efficacy was demonstrated in CD but recommended the term “achieving" over “inducing and maintaining" clinical response and remission for the indication (see Sections 7.9.1 and 12.3 of this CDTL Review; see also the CD Clinical Review by Klaus Gottlieb).

The CD Clinical Reviewer recommended that after the initial doses at Weeks 0, 2, and 6, the Q8W dosing regimen be the recommended dosing regimen because there was no difference in efficacy appreciated between the Q8W and Q4W dosing regimens. (See Section 12.3 of this CDTL Review.)

Key Subgroup Analyses - Maintenance

The subgroup analyses below show results for the Q8W arm and placebo. The Q8W dosing regimen is the recommended dosing regimen. Also, the subgroup analyses for Durable Clinical Remission are not shown as results were not statistically significant for the pre-specified analysis of Durable Clinical Remission as a secondary endpoint in the overall population.

Inadequate Response, Loss of Response, or Intolerance to a TNFα-Antagonist: The treatment differences for the primary endpoint of clinical remission at Week 52 and the first secondary endpoint of CDAI-100 Response at Week 52 were numerically lower in the subgroup of patients with an inadequate response, loss of response, or intolerance to a TNFα-antagonist than in the subgroup of patients with no prior use of a TNFα-antagonist. The treatment difference for the second secondary endpoint of corticosteroid-free remission was numerically higher in the subgroup of patients with an inadequate response, loss of response, or intolerance to a TNFα-antagonist than in the subgroup of patients with no prior use of a TNFα-antagonist. See table below.

Table 27. Subgroup Analysis - Inadequate Response, Loss of Response, or Intolerance to a TNFα-Antagonist vs. No Prior Use of a TNFα-Antagonist (C13007 Maintenance)

Endpoint	TNFα-Antagonist					
	Inadequate Response, Loss of Response, or Intolerance			No Prior Use		
	PBO	VDZ Q8W	Δ	PBO	VDZ Q8W	Δ
Clinical Remission at Wk 52	12.8% (10/78)	28.0% (23/82)	**15.2%**	26.8% (19/71)	51.5% (34/66)	**24.8%**
CDAI-100 Response at Wk 52	20.5% (16/78)	29.3% (24/82)	**8.8%**	38.0% (27/71)	60.6% (40/66)	**22.6%**
Corticosteroid-free Clinical Remission	0% (0/38)	24.4% (10/41)	**24.4%**	27.5% (11/40)	39.5% (15/38)	**12.0%**

Source: Page 250 of the C13007 Study Report

US Protocol Criteria The treatment differences for each of the three endpoints (the primary endpoint of clinical remission at Week 52, the first secondary endpoint of CDAI-100 Response at Week 52, and the second secondary endpoint of corticosteroid-free remission) was numerically lower in the subgroup of patients that met US Protocol Criteria[4] than in the subgroup of patients that did not meet US Protocol Criteria. See table below.

Table 28. Subgroup Analysis - Met US Protocol Criteria (Yes vs. No) (C13007 Maintenance)

Endpoint	Met US Protocol Criteria					
	Yes			No		
	PBO	VDZ Q8W	Δ	PBO	VDZ Q8W	Δ
Clinical Remission at Wk 52	14.1% (11/78)	28.8% (23/80)	**14.6%**	29.3% (22/75)	50.0% (37/74)	**20.7%**
CDAI-100 Response at Wk 52	25.6% (20/78)	28.8% (23/80)	**3.1%**	34.7% (26/75)	59.5% (44/74)	**24.8%**
Corticosteroid-free Clinical Remission	5.0% (2/40)	18.2% (8/44)	**13.2%**	26.2% (11/42)	47.4% (18/38)	**21.2%**

Source: Pages 36, 37, and 38 of the Response to IR received August 26, 2013

Baseline Concomitant Immunomodulator Use: The treatment difference for the primary endpoint of clinical remission at Week 52 was similar in the two subgroups. The treatment differences for the first secondary endpoint of CDAI-100 Response at Week 52 and for the second secondary endpoint of corticosteroid-free clinical remission were numerically higher in the subgroup with baseline concomitant immunomodulator use than in the subgroup without baseline concomitant immunomodulator use. See table below.

Table 29. Subgroup Analysis - Baseline Concomitant Immunomodulator Use (Yes vs. No) (C13007 Maintenance)

Endpoint	Baseline Concomitant Immunomodulator Use					
	Yes			No		
	PBO	VDZ Q8W	Δ	PBO	VDZ Q8W	Δ
Clinical Remission at Wk 52	30.6% (15/49)	46.0% (23/50)	**15.4%**	17.3% (18/104)	35.6% (37/104)	**18.3%**
CDAI-100 Response at Wk 52	38.8% (19/49)	58.0% (29/50)	**19.2%**	26.0% (27/104)	36.5% (38/104)	**10.6%**
Corticosteroid-free Clinical Remission	19.2% (5/26)	47.8% (11/23)	**28.6%**	14.3% (8/56)	25.4% (15/59)	**11.1%**

Source: Pages 258-259 of the C13007 Study Report

Demographic and Baseline Characteristics: The Clinical Reviewer noted that the results were consistent across age, gender, race, geographic region, duration of disease, and baseline disease activity (see CD Clinical Review).

The CD Clinical Reviewer noted that the above subgroup analyses should be interpreted with caution because they were post hoc and were based on small sample sizes. The Secondary Statistics Reviewer noted that that the subgroup analyses showed an expected variability of the treatment effect and should be viewed with caution due to their exploratory nature. The Secondary Statistics Reviewed also noted that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

Other Analyses - Maintenance

Subgroup Analysis (Entry from Cohort 1 vs. Cohort 2): The Primary Statistical Reviewer noted that a larger treatment difference was observed in patients that entered from Cohort 2 than in patients that entered from Cohort 1. The Secondary Statistical Reviewer noted that different presentations of the patient populations for the two induction cohorts were inevitable (because of the limitation of enrolling approximately 50% of patients who had failed TNFα antagonist therapies in Cohort 1 and the sequential enrollment of Cohort 2). The Secondary Statistics Reviewer further noted that some variability in the treatment effect across subgroups was to be expected, and that the analyses should be viewed with caution due to their exploratory nature.

Sensitivity Analyses Using Different Imputation Methods on the Missing Data: The Secondary Statistics Reviewer noted that extensive sensitivity analyses using different imputation methods on the missing data were requested by the Agency and conducted by the Applicant, and that all the results showed a favorable treatment effect for vedolizumab compared to placebo.

7.10 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical standpoint.

See Section 12.3 of this CDTL Review for a summary of the main revisions to the Applicant's proposed Indications and Usage, Dosage and Administration, and Clinical Studies sections of the label.

8. Safety

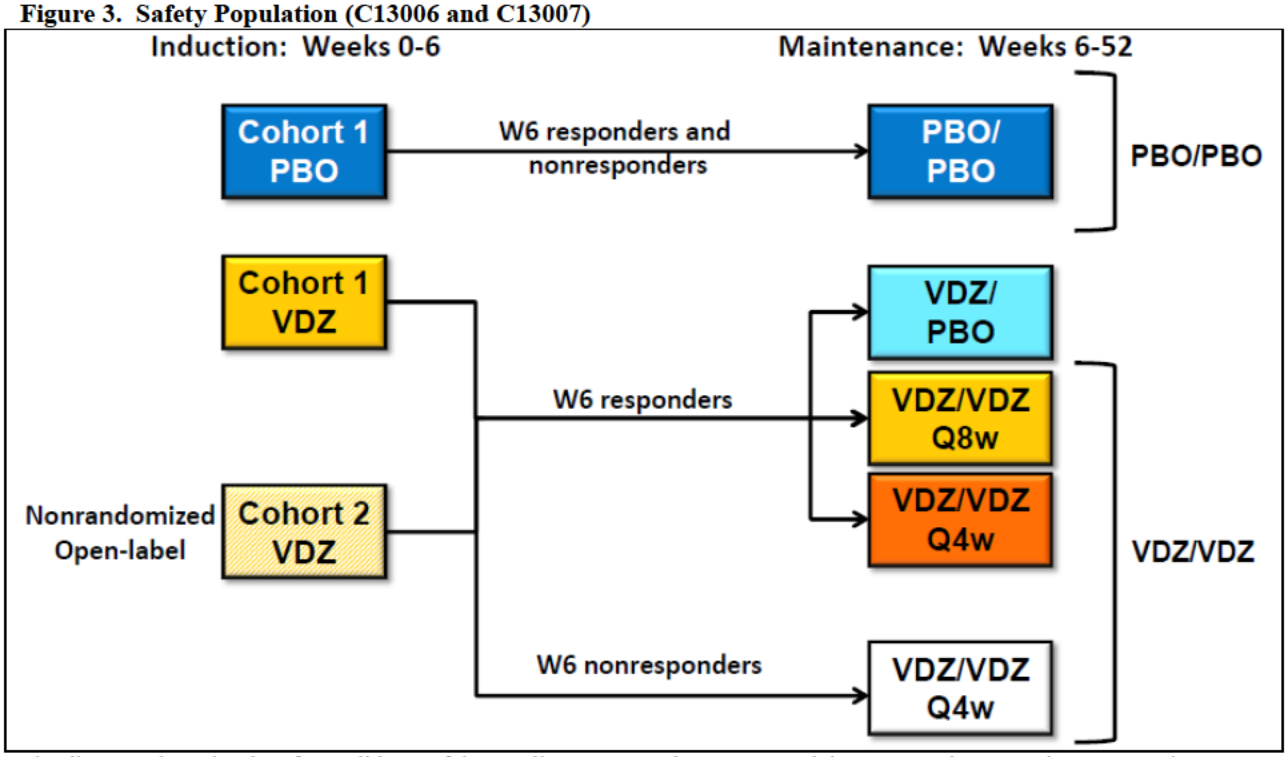
The reader is referred to the Clinical Reviews by Laurie Muldowney and Klaus Gottlieb for complete information.

8.1 Issues

Overall safety data are presented from the total of 3,326 subjects that received ≥ 1 dose of vedolizumab. Data from UC and CD patients are combined in these analyses.

Comparative safety data from the 1,434 patients who received vedolizumab only throughout the induction and maintenance trials for UC (C13006) and CD (C13007) (VDZ/VDZ) were compared to the 297 patients who received only placebo (PBO/PBO) and the 279 patients who received vedolizumab during induction and placebo during the maintenance phase (VDZ/PBO) (see the figure below).

Figure 3. Safety Population (C13006 and C13007)



The diagram above is taken from Slide 64 of the Applicant's December 9, 2013 Advisory Committee Meeting Presentation.

8.1.1 Exposure

Exposure data are summarized in the table below (based on a data cutoff date of June 27, 2013).

Table 30. Total Number of Patients by Duration of Dosing and Number of Infusions (Vedolizumab)

Duration of Dosing (Total Number of Patients):						
≥ 1 dose	≥ 6 mo.	≥ 12 mo.	≥ 18 mo.	≥ 24 mo.	≥ 36 mo.	≥ 48 mo.
3326	2022	1418	1162	906	407	40
Number of Infusions with 4-Week Follow-up (Total Number of Patients):						
≥ 1	≥ 6	≥ 12	≥ 18	≥ 24	≥ 36	≥ 48
3280	2196	1589	1228	1004	532	116

Table modified from Clinical Review by Laurie Muldowney.

8.1.2 Safety Findings

Deaths:

There were 12 deaths in patients receiving vedolizumab; the Clinical Reviewers concluded that none of the deaths were related to the study drug. See the Clinical Reviews.

Serious Adverse Events:

SAE's were reported in 19% of patients in the VDZ/VDZ group versus 13% in the PBO/PBO group and 15% in the VDZ/PBO group. The most frequently reported SAE's were related to the underlying disease and included CD (7% in VDZ/VDZ, 4% in PBO/PBO, and 3% in VDZ/PBO) and UC (3% in VDZ/VDZ, 3% in PBO, PBO, and 3% in VDZ/PBO).

Infections:

As there have been no cases of PML reported, one focus of the safety review was to determine if infections, particularly serious infections, are increased with vedolizumab treatment versus placebo or with cumulative vedolizumab dosing.

In the comparative safety data, infections overall were higher in the VDZ/VDZ group than the PBO/PBO group (43% vs. 35%), but serious infections were similar across groups (4% in VDZ/VDZ, 3% in PBO/PBO, and 3% in VDZ/PBO).

The most commonly reported infections were classified as upper respiratory tract infections (high level term) (24% VDZ/VDZ vs. 17% PBO/PBO) and appear to have driven the difference in frequency of overall infections between the VDZ/VDZ and PBO/PBO groups.

Serious infections occurred more frequently in CD (C13007) than in UC (C13006). In CD, serious infections were reported at a rate of 6% in VDZ/VDZ, 3% in PBO/PBO, and 3% in VDZ/PBO. In UC, serious infections were reported at a similar frequency between groups (2% in VDZ/VDZ; 3% in PBO/PBO, and 3% in VDZ/PBO).

The safety database was also evaluated for opportunistic infections. Systemic infections from enteric pathogens occurred in very small numbers, so comparisons were difficult to make. Fifty-one patients reported Herpes viral infections, but none were reported as 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% VDZ/PBO, 2% PBO/PBO, and 3% VDZ/VDZ).

No clear relation of these infections to number of infusions or to concomitant immunosuppressant use was found.

PML Risk Estimation:

Using the "Rule of Three,"[9] the worst possible scenario (i.e., the 95% upper bound of the true rate of PML) can be calculated based on the size of the safety database if no events are observed. Since no PML cases were observed in the 3,326 subjects that received one or more infusions, the true rate of PML will be lower than 0.9 in 1,000 with 95% confidence in patients that received one or more infusions. Similarly, since no PML cases were observed in the 1,004 patients that received 24 or more infusions, the true rate of PML will be lower

[9] The "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 (Jovanovic, B.D. and Levy, P.S. A Look at the Rule of Three. The American Statistician 1997;51(2):137-139).

than 2.99 in 1,000 with 95% confidence in patients that received 24 or more infusions. [Note that if the calculation is based on the number of patients that were exposed for 24 or more months (i.e., 906 patients) (instead of the number of patients that received 24 or more infusions), the true rate of PML will be lower than 3.31 in 1,000 with 95% confidence in patients that were exposed for 24 or more months.]

It is important to note that the safety database provides a comparison of the PML risk of vedolizumab to a benchmark rate (e.g., 2.99 in 1,000), but does not provide a comparison of the PML risk with vedolizumab to the PML risk with natalizumab. Thus, it will be difficult to infer that one drug has a more desirable risk profile than the other; any comparisons of risk between vedolizumab and natalizumab will be crude and should be interpreted with caution. Additional limitations are that vedolizumab Phase 3 trials sampled from a different population (CD or UC patients) than that from which natalizumab's PML risk was estimated in the natalizumab clinical trials (approximately two-thirds were MS patients, and one-third were CD patients) and that from which natalizumab's PML risk was estimated based on natalizumab postmarketing data (approximately 99% MS patients and 1% CD patients).

Other Safety Issues:

Hypersensitivity (several cases of urticaria and at least one case of anaphylaxis) were reported with vedolizumab use. Infusion-related reactions occurred at a rate of approximately 4% in patients receiving vedolizumab.

There was no clear increase in risk in carcinogenicity; however, long-term follow-up data would be necessary to reliably assess the risk of carcinogenicity.

Risk Assessment and Minimization for PML (RAMP) Program Findings:

No cases of PML have been identified in the 2,927 patients monitored through the RAMP program (as of June 28, 2013) (see Clinical Reviews). A total of 290 (10%) patients reported at least one abnormality on the subjective PML checklist; 64 had abnormal findings identified on the objective PML checklist. Fifty-eight MRIs were performed and 86 cases have been adjudicated by the independent adjudication committee (IAC). Five lumbar punctures have been performed. No cases of PML were identified (see Clinical Reviews).

Common Adverse Events:

Common AE's were reported in 84% of patients in the VDZ/VDZ group versus 78% in the PBO/PBO group and 84% in the VDZ/PBO group.

The most commonly reported AEs occurring in at least 5% of patients in the VDZ/VDZ group and at a higher rate than the PBO/PBO group were nasopharyngitis (13% in VDZ/VDZ vs. 7% in PBO/PBO vs. 10% in VDZ/PBO), headache (12% vs. 11% vs. 15%), arthralgia (12% vs. 10% vs. 13%), nausea (9% vs. 8% vs. 9%), pyrexia (9% vs. 7% vs. 11%), upper respiratory tract infection (7% vs. 6% vs. 7%), fatigue (6% vs. 3% vs. 5%), and cough (5% vs. 3% vs. 4%) (see Clinical Reviews).

A larger proportion of patients reported at least one infection in the VDZ/VDZ group (43%) than the PBO/PBO group (35%). The most commonly reported infections were classified as upper respiratory tract infections (high level term) (17% PBO/PBO; 24% VDZ/VDZ) and appears to have driven the difference in frequency of infections between the VDZ/VDZ and PBO/PBO groups. Systemic infections from enteric pathogens occurred in very small numbers, so comparisons are difficult to make. 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% VDZ/PBO, 2% PBO/PBO, and 3% VDZ/VDZ).

8.2 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

A PMR is recommended for a postmarketing, prospective, observational, cohort study of vedolizumab versus other agents for inflammatory bowel disease. The study's primary outcome is serious infections. Secondary outcomes include, but are not limited to, progressive multifocal leukoencephalopathy (PML), malignancy, and specific infections including gastrointestinal and upper respiratory infections. Concise case definitions and validation algorithms for both primary and secondary outcomes will be specified. The choice of appropriate comparator population(s) and estimated background rate(s) relative to vedolizumab-exposed patients will be justified; and the primary comparator population for the primary objective will be clearly defined. The study will be designed 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. The protocol will ensure that there will be an adequate number of patients with at least 24 months of vedolizumab exposure. (See **Other PMR #1** in Section 13.5 of this CDTL Review.)

A PMC is recommended for the sponsor to 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. (See Clinical PMC #1 in Section 13.6.1 of this CDTL Review.)

The DPV Reviewer recommended that we request for a period of two years, that the sponsor submit all cases of serious infections, possible cases of progressive multifocal leukoencephalopathy (PML), liver injury, and malignancies reported with vedolizumab as 15-day alert reports, and that the sponsor provide detailed analyses of clinical study and post-marketing reports of serious infections, possible cases of PML, liver injury, and malignancy as adverse events of special interest in the sponsor's Periodic Benefit-Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of vedolizumab as well as relative to the prior PBRER. Medical literature reviews for case reports/case series of serious infections, possible cases of PML, liver injury, and malignancy reported with vedolizumab should also be provided in the PBRER. (See DPV Review and Section 13.3 of this CDTL Review.)

The DRISK Reviewer concluded that risk mitigation measures beyond professional labeling are not warranted for vedolizumab at this time. The DRISK Reviewer noted that while the potential risk of PML cannot be completely ruled out, the available clinical and nonclinical data to-date, as well as the mechanism of action, suggest that vedolizumab is not associated with the risk of PML. The DRISK Reviewer noted that the benefit-risk profile for vedolizumab is favorable and the risks can be mitigated through professional labeling (see Section 12.3 of this CDTL Review), enhanced pharmacovigilance (see Section 13.3 of this CDTL Review), continuation of the open label extension study (see **Clinical PMC #1** in Section 13.6.6 of this CDTL Review), and the postmarketing observational study (see **Other PMR #1** in Section 13.5 of this CDTL Review). The DRISK Reviewer noted that if a case of PML is reported in the postmarketing setting that is determined to be associated with the administration of vedolizumab, the benefit-risk profile and risk management strategy will need to be re-evaluated for vedolizumab. (See DRISK Review.)

9. Advisory Committee Meeting

A Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was convened to discuss this application on December 9, 2013.

The questions posed to the committee, the results of voting, and a summary of the discussion that took place are 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)

      Voting Results: YES=12; NO=9; ABSTAIN=0

      Discussion: The majority of the committee voted that the data support the efficacy of vedolizumab for the proposed CD induction indication and noted that the 10 week data were convincing. Those voting "No" commented that the data presented by FDA showed that only one primary endpoint was met and the totality of the 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)

      Voting Results: YES=19; NO=1; ABSTAIN=1

      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." 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.

      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)

   Voting Results: YES=21; NO=0; ABSTAIN=0

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)

   Voting Results: YES=1; NO=19; ABSTAIN=1

   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.

   Voting Discussion: A=13; B=8; C=0

   Discussion**:** The majority of the members agreed that the benefits outweigh the potential risks of vedolizumab to support the approval for the proposed UC population that have failed steroids or immunosuppressants or TNF α-antagonists, and commented that restrictions would be burdensome in clinical practice**.** The Members who voted for "B" noted that patients failing steroids have other options. One member who had originally voted for "B" subsequently noted during the explanation of the vote that he wanted to vote for "A." 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.

Voting Results: A=14; B=6; C=1

Discussion: The majority of the committee agreed that the benefits outweigh the potential risks of vedolizumab to support approval for the proposed CD population that have failed steroids or immunosuppressants or TNFα-antagonists for the same reasons as the UC indication. Those who voted for "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.

Discussion: The committee members commented that it is important to quantify PML risk and to monitor other infections in addition to PML. The committee also noted that post-market risk mitigation strategies should not be burdensome for the practitioners. It was also suggested that self- reported adverse events registries could also be considered. Please see the transcript for details of the committee discussion.

10. Pediatrics

The application was presented to the Pediatric Research Committee (PeRC) on January 8, 2014.

The PeRC recommendations are summarized below.

- UC: The PeRC agreed with the Division on a partial waiver in pediatric patients aged birth to less than 5 years because studies would be impossible or highly impractical. The PeRC agreed with the Division on a deferral in pediatric patients aged 5 to less than 17 years because adult studies have been completed and the product is ready for approval.

- CD: The PeRC agreed with the Division on a partial waiver in pediatric patients aged birth to less than 6 years because studies would be impossible or highly impractical. The

PeRC agreed with the Division on a deferral in pediatric patients aged 6 to less than 17 years because adult studies have been completed and the product is ready for approval.

- Juvenile Toxicology Studies: The PeRC agreed to the addition of juvenile toxicology studies, which will not affect the proposed clinical study timeline.

See Section 13.4 of this CDTL Review for PREA PMR wording.

11. Other Relevant Regulatory Issues

11.1 QT Evaluation

The reader is referred to the QT-IRT Consult Review by Qianyu Dang for complete information.

The QT-IRT Reviewer concluded the following based on Study 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"):

> No large QTc prolongation effect of MLN0002 600 mg Process B and MLN0002 600 mg Process C was detected in this study. The largest upper bounds of the 2-sided 90% CI for the mean difference between MLN0002 600 mg Process B and MLN0002 600 mg Process C and placebo were 11.7 and 10.6 ms, respectively.
>
> In this randomized, placebo-controlled, double-blind, parallel-group study of a single dose of i.v. 600 mg MLN0002, 87 healthy subjects received a single i.v. dose of 600 mg Process B MLN0002, a single i.v. dose of 600 mg Process C MLN0002 and a single i.v. dose of placebo. An overall summary of findings is presented in Table 1.

Table 31. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MLN0002 600 mg (Process B and Process C) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Day	ΔΔQTcF (ms)	90% CI (ms)
MLN0002 Process B	8	5.7	(-0.3, 11.7)
MLN0002 Process C	8	4.7	(-1.1, 10.6)

*Multiple endpoint adjustment was not applied.

> The proposed therapeutic dose is 300 mg i.v. over approximately 30 minutes at 0, 2 and 6 weeks, then every 8 weeks thereafter. The single 300-mg dose of MLN0002 was selected for Part 1 of the study. The single 600-mg dose of MLN0002 in Part 2 is expected to provide similar MLN0002 concentrations as the predicted maximum MLN0002 concentration at steady state for the proposed therapeutic dose regimens. Extrinsic and intrinsic factors may have an effect on PK of MLN0002, resulting in a higher exposure than the level observed in this study (C13009). The potential effect of organ impairment and drug-drug interactions on the PK of MLN002 will be explored as part of the population pharmacokinetic analysis of Phase 3 data.

11.2 Office of Scientific Investigations (OSI) Audits

The reader is referred to the OSI Clinical Inspection Summary by Susan Leibenhaut for complete information.

Site Inspections:

Overview of Sites Inspected and Final Classifications:

An overview of the four sites inspected and final classifications are presented in the table below.

Table 32. Overview of Sites Inspected and Final Classifications

Investigator Location / Site No,	Study	No. pts*	Final Classification
Scott Lee Seattle, WA / 58045	C13006	15	VAI
	C13007	21	
	C13011	18	
Seema Dar San Antonio, TX / 58156	C13006	8	NAI
	C13007	3	
Gert Van Assche Leuven, Belgium / 04006	C13006	41	NAI
	C13007	32	
	C13011	19	
Zdenka Zadorova Praha, Czech Republic / 12019	C13006	9	NAI
	C13007	9	
	C13011	5	

*Number of patients enrolled.

Inspector's Key Findings:

The Inspector's key findings are summarized below by Clinical Investigator (CI):

Scott Lee:

- A Form FDA 483 was issued for the following violations and Dr. Lee adequately responded.
  - No phone calls were made to subjects who enrolled in protocols 13006 and 13007 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 Clinical Investigator (CI) stated that the calls were made but not documented.
  - A stool sample for the analysis of the Fecal Calprotectin was not collected in 12 subjects (out of 24 screened) 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.
  - 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.
    - For Protocol C13007, the CDAI scores were not calculated as specified in the protocol for 15 subjects (out of 21 enrolled). In his response, the CI attributed this to the fact that the site was using their usual guidelines for calculation of the CDAI and had not realized that the sponsor guideline differed from the site guideline.
- The violations noted above did not adversely affect data integrity or subject safety.
- The endpoints were calculated centrally by the sponsor.

Other CI's (Seema Dar; Gert Van Assche; Zdenka Zadorova):
- No significant regulatory violations were noted.
- No Form FDA 483 was issued.
- There was no evidence of underreporting of AEs.
- The source data for the primary efficacy data were able to be verified at the site.

Final Conclusion - Site Inspections:

For each of the four sites, OSI concluded that the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Sponsor Inspection:

Overview of Sponsor Inspection and Final Classification:

Monitoring for seven study sites was reviewed including procedures and systems used to collect data and calculate the primary endpoints for each of the clinical trials.

The OSI Review states that observations for the sponsor inspection are based on e-mail communications with the FDA field investigator, and that an addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR) from the sponsor inspection.

The final classification is pending at the time of this review; however, the sponsor inspection has a preliminary classification of NAI with the findings noted below and described in the study reports for Studies C13006 and C13007. The OSI Review states that an addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR) from the sponsor inspection.

Inspector's Key Findings:

No regulatory violations were noted and a Form FDA 483 was not issued. The calculations for the CDAI and Mayo scores conducted by the sponsor were compared with the line listings submitted with the BLA and provided to the FDA investigator and no discrepancies were noted. The sponsor monitoring was adequate. The OSI Reviewer noted that the sponsor

was not cited because they identified the problem, took corrective action and reported the occurrence in the clinical study reports. See below:

> The protocols required that the study sites use their own calculated CDAI and Mayo scores for subject care purposes and, in the case of Studies C13006 and C13007, the study site calculations also determined which subjects are randomized at Week 6 into the maintenance phase. The CDAI and Mayo scores at the end of each study were calculated centrally. In June of 2009, approximately six months after the first subjects were enrolled in each of the studies, during quarterly review of the data, Millennium noted discrepancies in the data. Millennium determined that study sites were not calculating the CDAI and Mayo scores correctly, resulting in some subjects being categorized incorrectly as responders or nonresponders. This "miscategorization" by the study sites resulted in some subjects being assigned into the incorrect arm for the maintenance study. For Study C13006, this occurred in 59 of 895 enrolled subjects. For Study C13007, this occurred in 107 of 1116 enrolled subjects. This "miscategorization" is described in detail in Sections 11.2.1-M of each report, "Primary Efficacy Endpoint, Maintenance."
>
> After discovering the miscalculations, Millennium took action by requesting that (b) (4) the study monitor, improve the review of the CDAI and Mayo scores. Millennium also conducted re-training for (b) (4) and their clinical research associates and updated the monitoring plan to include a more in depth overview and review of the CDAI and Mayo score calculations. In addition, Millennium created an in-depth Data Quality Initiative for the Gemini Program (which includes Studies C13006 and C13007). Within the Data Quality Initiative program, Millennium provided detailed instructions to (b) (4) to assure better monitoring, including closer review of primary endpoints (CDAI and Mayo calculations included).

Final Conclusion - Sponsor Inspection:

OSI concluded that the studies appear to have been conducted adequately, and the data generated by the sponsor may be used in support of the respective indications.

12. Labeling

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Lisa Khosla, dated August 20, 2013.

DMEPA concluded that the proprietary name of "Entyvio" was acceptable. This was communicated to the Applicant in the Proprietary Name Request Conditionally Acceptable Letter dated August 20, 2013, along with a statement that the proposed proprietary name of "Entyvio" will be re-reviewed 90 days prior to the approval of the BLA.

12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name (Entyvio) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Lisa Khosla, dated August 20, 2013.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The main revisions to the Applicant's proposed Physician Labeling are summarized below:

- Indications and Usage (Section 1 of Label): For UC, the Applicant's proposed wording of (b) (4) was replaced with "improving the endoscopic appearance of the mucosa"; (b) (4) For UC, the Applicant's proposed wording of "inducing and maintaining" clinical response and clinical remission was acceptable based on the results of the UC studies. However, for CD, the Applicant's proposed wording of (b) (4) clinical response and clinical remission was replaced with "achieving" clinical response and clinical remission (see Section 7.9 of this CDTL Review). The Applicant's proposed indicated population of patients that had failed steroids, immunomodulators, or TNFα-antagonists was accepted (rather than the more restrictive indicated population of patients that had failed immunomodulators or TNFα-antagonists); this is consistent with the recommendations of the Advisory Committee (see Section 9 of this CDTL Review). The Applicant's proposal that concomitant immunomodulators should not be restricted to induction only was accepted; this is consistent with the recommendations of the Advisory Committee (see Section 9 of this CDTL Review).

- Dosage and Administration (Section 2 of Label): After the initial doses at Weeks 0, 2, and 6, the Q8W dosing regimen is the recommended dosing regimen for both UC and CD because in each of the disease populations, (b) (4) (see Sections 7.8.2 and 7.9.2 of this CDTL Review).

- Warnings and Precautions (Section 5 of Label): Rather than the Applicant's proposal to (b) (4) a separate sub-section titled "Progressive Multifocal Leukoencephalopathy" was created to discuss the risk. Statements were added explaining that while zero cases of PML were identified among patients with at least 24 months of exposure to vedolizumab, a risk of PML cannot be ruled out, and that no comparative safety claims to other integrin receptor antagonists can be made based on this data. In addition, a paragraph was added which advised the prescriber to monitor patients for any new onset, or worsening, of neurological signs and symptoms, and summarized the typical signs and symptoms of PML.

- Drug Interactions (Section 7 of Label): The Applicant's proposed statement (b) (4) was removed primarily because there are no data to support this recommendation. A statement to avoid concomitant use with natalizumab was added. Also, a statement to avoid concomitant use with a TNFα-antagonist was added.

- Clinical Studies (Section 14 of Label): The differences in entry requirements in the US versus outside the US were described (i.e., in the US, patients had to have failed an immunomodulator or TNFα-antagonist whereas outside the US, failure of a steroid only was sufficient for entry). For each of the trials, the proportions of patients receiving corticosteroids at baseline and receiving immunomodulators at baseline were included. Also, for each of the trials, the proportion of patients with inadequate response, loss of response, or intolerance to a TNFα-antagonist was included. (b) (4) (b) (4)

In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the DMPP Patient Labeling Review and the OPDP Labeling Review. The reader is referred to each of these reviews for complete information.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant on December 4, 2013 (see DMEPA Label and Labeling Review).

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

All of the review disciplines recommended an Approval action. This Reviewer concurs with the recommendations from each of the disciplines.

13.2 Risk Benefit Assessment

The benefit of vedolizumab in moderate to severe UC and CD has been established in the clinical trials. The potential risk of PML cannot be completely ruled out; however, the mechanism of action and the available clinical and nonclinical data to-date suggest that vedolizumab is not associated with the risk of PML.[10] The benefit-risk profile for vedolizumab is favorable and the risks can be mitigated through professional labeling (see

[10] See conclusions of DRISK Review by George Neyarapally.

Section 12.3 of this CDTL Review), enhanced pharmacovigilance (see Section 13.3 of this CDTL Review), continuation of the open label extension study (see Clinical PMC #1 in Section 13.6.6 of this CDTL Review), and the postmarketing observational study (see Other PMR #1 in Section 13.5 of this CDTL Review).[10] If a case of PML is reported in the postmarketing setting that is determined to be associated with the administration of vedolizumab, the benefit-risk profile and risk management strategy will need to be re-evaluated for vedolizumab.[10]

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

However, it should be noted that pharmacovigilance will be requested with the following language for the Approval Letter:

> We request that for a period of two years, you submit all cases of serious infections, possible cases of progressive multifocal leukoencephalopathy (PML), liver injury, and malignancies reported with ENTYVIO (vedolizumab) as 15-day alert reports, and that you provide detailed analyses of clinical study and post-marketing reports of serious infections, possible cases of PML, liver injury, and malignancy as adverse events of special interest in your Periodic Benefit-Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of ENTYVIO (vedolizumab) as well as relative to the prior PBRER. Medical literature reviews for case reports/case series of serious infections, possible cases of PML, liver injury, and malignancy reported with ENTYVIO (vedolizumab) should also be provided in the PBRER.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Postmarketing required pediatric studies under PREA are recommended for the current application, with the following language for the Approval Letter. Note that PREA PMR's #1 through #4 correspond to PMR's 1 through 4 in the Approval Letter.

> **REQUIRED PEDIATRIC ASSESSMENTS**
>
> Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.
>
> We are waiving the pediatric studies requirement for patients ages 0 to 4 years with moderately to severely active ulcerative colitis because necessary studies are impossible or highly impracticable.This is because there is a low incidence of the disease in this age group. We are waiving the pediatric studies requirement for

patients ages 0 to 5 years with moderately to severely active Crohn's disease because necessary studies are impossible or highly impracticable. This is because there is a low incidence of the disease in this age group.

We are deferring submission of your pediatric studies for ages 5 to 17 years (moderately to severely active ulcerative colitis) and for ages 6 to 17 years (moderately to severely active Crohn's disease) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

PREA PMR #1:

Conduct a juvenile animal toxicology study of 3 months duration in an appropriate species before initiation of the pediatric trials in patients 5 to 17 years of age.

Final Protocol Submission:	February 2015
Study Completion:	August 2015
Final Report Submission:	February 2016

PREA PMR #2:

Conduct a dose-ranging study to determine the pharmacokinetics/ pharmacodynamics, safety, and tolerability of Entyvio (vedolizumab) in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis or Crohn’s disease who have failed conventional therapy.

Final Protocol Submission:	March 2016
Study Completion:	July 2019
Final Report Submission:	July 2020

PREA PMR #3:

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

Final Protocol Submission:	August 2020
Study Completion:	May 2026
Final Report Submission:	May 2027

PREA PMR #4:

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

Final Protocol Submission:	August 2020
Study Completion:	June 2027
Final Report Submission:	June 2028

Submit the protocols to your IND 009125 with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

The following other postmarketing required study is recommended for the current application, with the following language for the Approval Letter. Note that Other PMR #1 corresponds to PMR 5 in the Approval Letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of serious infections (such as respiratory and gastrointestinal infections) or to identify the unexpected serious risks of progressive multifocal leukoencephalopathy (PML), and malignancies related to the use of ENTYVIO (vedolizumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

Other PMR #1:

A postmarketing, prospective, observational, cohort study of vedolizumab versus other agents for inflammatory bowel disease. The study's primary outcome is serious infections. Secondary outcomes include, but are not limited to, progressive multifocal leukoencephalopathy (PML), malignancy, and specific infections including gastrointestinal and upper respiratory infections. 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.

The timetable you submitted on April 14, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2014
Interim Report:	July 2018
Study Completion:	June 2021
Final Report Submission:	June 2022

Submit the protocol to your IND 009125 with a cross-reference letter to this BLA. Submit the final report to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical

trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

13.6.1 Clinical

The following clinical postmarketing commitment is recommended for the current application, with the following language for the Approval Letter. Note that Clinical PMC #1 corresponds to PMC 6 in the Approval Letter.

Clinical PMC #1:

Complete Clinical Trial C13008, an open-label trial to determine the long-term safety of Entyvio (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.

The timetable you submitted on April 03, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion:	March 2016
Final Report Submission:	March 2017

13.6.2 Maternal Health

The following maternal health postmarketing commitments are recommended for the current application, with the following language for the Approval Letter. Note that Maternal Health PMC's #1 and #2 correspond to PMC's 7 and 8 in the Approval Letter.

Maternal Health 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 Entyvio (vedolizumab) during pregnancy to an unexposed control population or collect Entyvio (vedolizumab) pregnancy exposure data by collaborating with an existing disease-based pregnancy registry.

The timetable you submitted on April 15, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2015
Study Completion:	May 2021
Final Report Submission:	May 2022

Maternal Health PMC #2:

Conduct a milk-only lactation study 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 timetable you submitted on April 15, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2015
Study Completion:	March 2018
Final Report Submission:	March 2019

13.6.3 Clinical Pharmacology

The following clinical pharmacology postmarketing commitments are recommended for the current application, with the following language for the Approval Letter. Note that clinical pharmacology PMC's #1 and #2 correspond to PMC's 9 and 10 in the Approval Letter.

Clinical Pharmacology PMC #1:

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.

The timetable you submitted on April 03, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2015
Study Completion:	March 2016
Final Report Submission:	March 2017

Clinical Pharmacology PMC #2:

Evaluate in a step-wise approach the disease-drug-drug interaction (Disease-DDI) potential for vedolizumab to indirectly affect the exposure of CYP substrate drugs by modulating pro-inflammatory cytokines in patients with ulcerative colitis and Crohn's disease who are treated with vedolizumab.

The timetable you submitted on April 03, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2015

Study Completion:	September 2019
Final Report Submission:	September 2020

13.6.4 Quality

The following Quality postmarketing commitments are recommended for the current application, with the following language for the Approval Letter. Note that Quality PMC's #1 through #9 correspond to PMC's 11 through 19 in the Approval Letter.

Quality PMC #1:

To perform additional testing to confirm the monoclonality of the master cell bank.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2014

Quality PMC #2:

To add osmolality testing to the vedolizumab drug product lot release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: September 2014

Quality PMC #3:

To add polysorbate 80 testing to the vedolizumab drug product lot release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2014

Quality PMC #4:

To develop a non-reducing SDS-based assay that is capable of providing quantitative data for the evaluation of size-related impurities and to implement this assay in the release and stability programs for vedolizumab drug substance and drug product after

sufficient data have been acquired to set appropriate acceptance criteria. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: February 2016

Quality PMC #5:

To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to vedolizumab, including procedures for accurate detection of binding antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2014

Quality PMC #6:

To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to vedolizumab, including procedures for accurate detection of neutralizing antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2014

Quality PMC #7:

To develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the vedolizumab drug substance release program. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2017

Quality PMC #8:

To re-evaluate vedolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2016

Quality PMC #9:

To re-evaluate vedolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

The timetable you submitted on May 05, 2014, states that you will conduct this study according to the following schedule:

Final Study Report Submission: December 2018

13.6.5 Microbiology Quality - Drug Substance

The following Microbiology Quality - Drug Substance postmarketing commitments are recommended for the current application, with the following language for the Approval Letter. Note that Microbiology Quality - Drug Substance PMC's #1 and #2 correspond to PMC's 20 and 21 in the Approval Letter.

Microbiology Quality Drug Substance PMC #1

To conduct a maximum hold time study for the formulated drug substance using representative containers. If low endotoxin recovery is found in the formulated drug substance during the maximum hold time study, either hold times will be reevaluated or an alternative method to measure endotoxin in formulated drug substance will be developed and validated.

The timetable you submitted on April 03, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2014

Microbiology Quality Drug Substance PMC #2

To verify the endotoxin recovery results for the (b) (4) and establish action limits for this solution once the results are confirmed by a validated method. If low endotoxin recovery is found, maximum hold times (b) (4)

The timetable you submitted on April 03, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2014

13.6.6 Microbiology Quality - Drug Product

The following Microbiology Quality - Drug Product postmarketing commitments are recommended for the current application, with the following language for the Approval Letter. Note that Microbiology Quality - Drug Product PMC's #1 through #3 correspond to PMC's 22 through 24 in the Approval Letter.

Microbiology Quality Drug Product PMC #1

To assess the sensitivity of the current dye and microbial ingress assays for container closure integrity testing. The studies will be conducted by perforating the container closure system with needles and capillaries that vary in internal diameter down to an internal size of (b) (4). If it is determined that the current methods are not sensitive to perforations of (b) (4) the methods will be optimized as necessary for the detection of breaches (b) (4)

The timetable you submitted on April 28, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2014

Microbiology Quality Drug Product PMC #2

To conduct studies to qualify the endotoxin kinetic turbidometric LAL assay for testing vedolizumab bulk drug product and finished drug product. Qualification studies will be conducted on three lots of endotoxin-spiked undiluted bulk drug product and finished drug product held under held under worst case hold conditions in the relevant containers. These studies should demonstrate acceptable endotoxin recoveries of spiked endotoxin initially and after worse case hold conditions. In the event kinetic turbidometric qualification studies demonstrate that acceptable endotoxin recoveries from the spiking studies are not achieved, the USP <151> rabbit pyrogen method will be used to release the finished drug product.

The timetable you submitted on April 28, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2014

Microbiology Quality Drug Product PMC #3

To conduct studies to qualify an endotoxin assay for Vedolizumab Drug Product (b) (4) Validation will be conducted with (b) (4) held under worst case conditions in the relevant containers. The qualified methods will be implemented for routine testing of the drug product (b) (4)

The timetable you submitted on April 28, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2014

13.7 Recommended Comments to Applicant

None.

APPENDIX 1

Criteria for Inadequate Response with, Loss of Response to, or Intolerance to TNFα Antagonists or Immunomodulators, and Criteria for Inadequate Response with, Intolerance to, or Dependence on Corticosteroids

Ulcerative Colitis (Study C13006)

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-mercaptopurine (≥0.75 mg/kg) OR
- History of intolerance of at least one immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection)

TNFα antagonists
- 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
- Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) OR
- History of intolerance of infliximab (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

Corticosteroids (only applicable to patients outside the US; who may have been enrolled on the basis of corticosteroid treatment history)
- 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).

Crohn's Disease (Studies C13007 and C13011)

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-mercaptopurine (≥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 one immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection)

TNFα 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 maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) OR
- History of intolerance of infliximab (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

Corticosteroids (only applicable to patients outside the US; who may have been enrolled on the basis of corticosteroid treatment history)

- 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).

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/s/

ANIL K RAJPAL
05/20/2014