CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Review

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	BLA 125476
Applicant Name	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) Name**	Entyvio / vedolizumab
Dosage Forms / Strength	Lyophilized Powder for Injection
Proposed Indication(s)	1. Moderate to Severe Ulcerative Colitis (Induction and Maintenance) 2. Moderate to Severe Crohn's Disease (Induction and Maintenance)
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Klaus Gottlieb, MD Laurie Muldowney, MD
Statistical Review	Division of Biometrics III: Milton Fan, PhD/Freda Cooner, PhD
Pharmacology Toxicology Review	Tamal Chakraborti, PhD
CMC Review/OBP Review	Qing Zhou/Rashmi Rawat CMC Microbiology Quality: Steven Fong/Reyes Candau-Chacon
Clinical Pharmacology Review	Lanyan Fang, PhD/Yow-Ming Wang, PhD
OPDP	Adewale Adeleye
OSI	Susan Leibenhaut, MD
CDTL Review	Anil Rajpal, MD
OSE/DMEPA	Lisa Khosla
OSE/DRISK	George Neyarapally, PharmD, MPH/Reema Mehta, Pharm D, MPH/ Claudia Manzo, PharmD
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OSE/OPE	Mark Avigan, MD CM
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Division of Medical Policy Programs	Nathan Caulk

OND=Office of New Drugs
OPDP=Office of Professional Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

Takeda Pharmaceuticals U.S.A., proposes the following indications for this initial Biologics License Application (BLA) for Entyvio (vedolizumab), a recombinant, humanized IgG1 monoclonal antibody directed against the human lymphocyte α4β7 integrin:

- Ulcerative Colitis: "…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."

- Crohn's Disease: "…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."

My review will focus on key review issues that were presented and discussed at an Advisory Committee meeting (Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee) on December 9, 2013. These include a safety issue associated with the entire Entyvio program and an efficacy issue associated with the Crohn's development program.

With regard to safety, another integrin antagonist approved for treatment of Crohn's disease, Tysabri (natalizumab), is associated with progressive multifocal leukoencephalopathy (PML). Tysabri has a Risk Evaluation and Mitigation Strategy (REMS), and is available only under a special restricted distribution program. Differences in integrin targeting between Tysabri and Entyvio, and the absence of PML within the Entyvio development program raised review questions regarding whether there was adequate safety information available to support approval of Entyvio without a REMS.

Entyvio's efficacy in Crohn's disease (CD) was evaluated in two induction trials and one maintenance trial. The favorable induction outcome at 6 weeks observed in one trial was not replicated in the second trial, which enrolled a higher proportion of patients who had failed prior TNFα antagonist therapy than the other trial. However, a statistically significantly higher remission rate was noted at the 52 week assessment in patients treated with Entyvio in the "maintenance" trial that enrolled patients who had achieved a clinical response or a clinical remission in one of the induction trials or with open label treatment with vedolizumab. Typically, a maintenance of remission indication is granted if a product has been shown to induce a remission that is then sustained over time with continued treatment, in the same patient. Ideally the maintenance trial design randomizes patients who have achieved remission

between continued treatment with study drug vs. discontinuation of treatment. In the Entyvio maintenance trial, a prespecified analysis of a secondary endpoint "durable remission", which defined treatment success as having remission at entry (successful induction 6 weeks after starting treatment) AND at study completion (52 weeks) AND in ≥ 80 % of interim assessments on study (performed every 4 weeks), was NOT statistically significant.

The lack of replication of induction of remission at 6 weeks and the failure to demonstrate a statistically significant "durable clinical remission" was presented to an Advisory Committee, and the majority of panelists voted to approve Entyvio for both the Crohn's disease induction and maintenance indications. Effective therapies for CD are limited and that the Committee members were persuaded by the evidence of remission at 6 weeks in one induction trial and the evidence of remission at 52 weeks in the maintenance trial. The evidence of remission at two different time points in two different trials supports that Entyvio has a clinically beneficial impact on this disease. However, the reviewers did not agree that the data presented in this BLA support a "maintenance of remission" indication, based on the evidence that Division of Gastroenterology and Inborn Errors Products (DGIEP) has been requiring of other applicants to support such an indication. How to appropriately describe the efficacy of Entyvio demonstrated in the CD trials as an indication in product labeling was a review challenge, and involved multiple discussions with the applicant. The applicant argued that DGIEP has not required documentation of remission in ≥80 % of interim study assessments for maintenance of remission indications for ulcerative colitis (UC). However, remission in ulcerative colitis is assessed, in part, with endoscopy, which is not repeated between baseline and end of study in maintenance trials. In addition, "durable remission" was the prespecified endpoint in the Entyvio maintenance trial; a remission analysis limited to baseline (Week 6) and 52 week assessment was not.

2. Background

In this section, I have summarized the regulatory history relevant to the safety and efficacy review issues described above.

Safety. Tysabri (natalizumab), which has been associated with a serious risk of PML from JC virus, is an integrin antagonist that binds to the α4 subunit of both α4β7 and α4β1 integrins. Tysabri's interaction with α4β1 integrins, which are found in the CNS, is believed to increase PML risk. Entyvio was designed to bind to α4β7 integrins and to have a targeted impact limited to α4β7 interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and fibronectin.

Tysabri was approved in the US in November 2004, and subsequently withdrawn in February 2005 after 2 PML cases were identified in a multiple sclerosis (MS) trial and one case was retrospectively identified in a Crohn's disease (CD) trial. It returned to the market in June 2006, with restricted distribution. The two MS cases were identified among 1869 MS patients treated with Tysabri for a median of 120 weeks. The single CD case was identified among 1043 CD patients treated with Tysabri in a clinical trial setting. As of September 2012, the estimated cumulative PML incidence (across the two indications) was 2.63 per 1000 (95% CI 2.2-2.9). Division of Epidemiology II (DEPI) provided an estimated incidence of PML in CD patients treated with Tysabri, based on the two confirmed postmarketing PML cases that have been

identified (from FDA Adverse Event Reporting System, FAERS) in CD patients treated with Tysabri and an exposure estimate based on Tysabri sales data. As stated in the FDA's AC meeting Briefing package, "The estimated incidence of PML for NTZ-treated CD patients is 1.77 per 1000 patients. The estimated incidence rate is 1.72 per 1000 patient years of exposure; in other words, if you exposed 500 patients to NTZ for an average of two years, you would expect to see 1.72 cases of PML."

Risk factors that increase the risk of PML in patients treated with Tysabri include 1) longer treatment duration (>2 years), 2) prior treatment with an immunosuppressant, and 3) presence of anti-JCV antibodies.

Information available on Tysabri's PML risk informed the FDA's advice on the Entyvio clinical development plan. The IND sponsor pointed to differences in receptor binding targets between Entyvio and Tysabri to justify their proposals for clinical trial eligibility criteria, and to urge the FDA to reduce the number and duration of exposures to Tysabri FDA required for BLA review. A closed session of the GIDAC and DSaRM was convened on July 20, 2011 to discuss these development program issues. The Committee did not reach consensus on the acceptable size of the pre-approval safety database; however, the committee considered 24 months a minimum duration for adequate assessment. The Committee did not support relaxing the US clinical trial site eligibility criteria to allow entry of patients who had not been previously treated with TNF alpha antagonists or immunosuppressant, and did not support relaxing restrictions on use of concomitant immunosuppressants during the induction phase of study. These restrictions were not observed at the ex-US sites that participated in the Entyvio program.

The FDA and the IND sponsor met after the AC, on September 6, 2011. The discussion points included the following:

1) FDA disagreed with the sponsor's proposal that 1400 patients evaluated for a minimum duration of 12 months would be adequate for BLA submission. The FDA stated that the sponsor should study "at least 1000 patients for a minimum number of 24 infusions. With this safety database, the 95% CI upper bound for the true PML event rate after 24 or more infusions would be 3/1000 (based on the Rule of 3) if no events are observed. A substantial proportion of these patients should have been exposed to 36 infusions or more." The number of infusions was emphasized (vs. number of months) because "a substantial proportion of the patients in the maintenance phase of the clinical trials will be receiving Q 8 week treatment for approximately one year. If the Q 4 week treatment was the approved dose, then an inadequate number of patients treated at that dose may be in the safety database at the time of BLA filing if the number is based on months of exposure rather than number of infusions."
2) The FDA stated that the substantial proportion of patients with a history of immunosuppressant use or concomitant immunosuppressant use that would be anticipated to enroll in the trials would be expected to result in an increased risk for PML. If a PML event occurred, the size of the safety database and duration of exposure adequate for filing would need to be revisited.
3) The sponsors proposed to present unblinded safety data in approximately 900 patients treated for at least 18 months at a pre-BLA meeting, and stated that they disagreed with basing the duration of exposure on number of infusions instead of number of months.

In a July 24 and 25, 2012, Type C End of Phase 3 meeting, the following points were discussed regarding safety:

1) IND sponsor again asked for agreement that the duration of exposure could be based on number of months instead of number of infusions. The FDA disagreed, for the same reasons given at the prior meeting. The sponsor proposed that safety data on 1000 patients for a minimum duration of 24 months, combined with a post-marketing risk management plan would be sufficient to support BLA submission. The FDA disagreed, noting that the proposal was similar to that made at the prior meeting, with the exception of a smaller number of patients exposed for at least 36 months: "Currently, you are proposing the following numbers of patients exposed (by number of months of exposure) (data cutoff date of 6 months prior to BLA filing date): ~1300 (≥ 12 months), ~950 (≥ 18 months), ~600 (≥ 24 months), and ~100 (≥ 36 months).[6] Previously, you had proposed the following numbers of patients exposed (by number of months of exposure) (data cutoff date relative to BLA filing date not provided): 1,400 (> 12 months), 900 (> 18 months), 575 (>24 months), and 280 (> 36 months)." The FDA reiterated its position for minimum safety database for BLA submission. After further discussion, the FDA stated, "data from at least 900 patients that received ≥ 24 infusions (with a minimum of 4 weeks of follow-up after the last infusion) would be required for us to conduct a review and present to an Advisory Committee." Earlier submission, in conjunction with a plan of submitting the desired target exposure as a safety amendment, would likely result in a clock extension.
2) The sponsor proposed a risk management strategy to include in the BLA submission, which included pharmacovigilance activities and risk minimization strategies such as labeling, a medication guide and a communication plan for prescribers and infusion centers. The FDA encouraged the sponsor to submit a proposed REMS in the BLA for full review, stating that input from an Advisory Committee on the proposed REMS would be necessary.

In the Pre-BLA meeting, which occurred on November 6, 2012, the sponsor proposed that the BLA submission would be timed such that "the majority of the safety database requested by the Division available for the Day 120 Safety Update." The FDA responded that "Due to the new requirements under FDUFA V for applications under the "Program", we cannot agree with your proposal. Your safety database at the time of original BLA submission must include data on at least 900 patients that received ≥24 infusions (with a minimum of 4 weeks of follow-up after the last infusion)."

Efficacy. Exploratory analyses of the CD trial data suggest that remission induction might have been replicated if the assessments had been performed at a later time point. Additional work in the pre-phase 3 period of clinical development may have defined when the treatment effect of vedolizumab would be maximized in CD. I will summarize the regulatory record of interactions between the IND sponsor and FDA from this perspective here.

In an April 18, 2008 type C meeting, the FDA's comments included the following:

> **"We recommend that you obtain more data in each disease population (ulcerative colitis [UC] and Crohn's disease [CD]) using the Process B material before initiating Phase 3 studies. First, because the proposed target populations in your Phase 3 studies have more severe disease (moderately to severely active UC and moderately to severely active CD) than the patients in the ongoing studies (mildly to moderately active UC and mildly to moderately active CD), we recommend that**

you study a range of doses and dosing frequencies in each target population in order to identify the optimal doses for each Phase 3 program. Second, because there is no proposed placebo-controlled study in CD using the Process B material and because the completed CD study did not meet its primary endpoint, more information about the time course of the clinical response in the target CD population may help to inform the optimal timing of assessments for efficacy endpoints in the design of the Phase 3 CD program."

In a June 5, 2008 type C meeting, FDA comments included:

It appears that the proposed target populations in your Phase 3 studies nominally have more severe disease (moderately to severely active UC and moderately to severely active CD) than the patients in the completed and ongoing studies (mildly to moderately active UC and mildly to moderately active CD). Conducting additional studies as recommended above in the target populations that you intend to study in Phase 3 may help you to select the optimal dose, dosing frequency, and timing of endpoints.

However, with regard to the CD program, the FDA did suggest earlier time points for induction assessment might be explored:

With regard to the primary endpoint for the CD induction trial, clinical remission at Week 6 appears to be reasonable. However, the results of your study in CD (L299-016) suggest that the placebo response may be increasing over time; thus, an earlier time point for the primary endpoint may be worth considering.

Discussion recorded in the meeting minutes included:

FDA noted that the clinical response observed with 2 mg/kg was reasonably good, and that it might be hard to improve the clinical response substantially with higher doses. Millennium stated that the primary goal of therapy is maintenance, not induction, and that the benefit-risk considerations are applicable to maintenance therapy, not induction therapy. Millennium emphasized that optimizing the induction dose should not be the focus, and stated that key considerations in the dose selection should be the higher HAHA incidence, persistence, and titers that are expected with lower doses. FDA questioned the plan to use a longer dosing interval rather than a lower dose to explore the dose response. FDA felt that the choice of dose and dosing interval was not that strongly supported from Phase 2 clinical data, and suggested Millennium test their hypotheses about the proposed dose and dosing interval in smaller studies prior to Phase 3. FDA stated that, while they could not concur that Millennium's choice of doses was well supported, the choice was not unreasonable to study; however, Millennium would be proceeding with their development program at their own risk.

The following excerpts from the regulatory record provide background on regulatory agreements regarding endpoints and analysis plan:

In a September 10, 2009 teleconference between the FDA and sponsor regarding the statistical analysis plan for the CD study C13007, the sponsor proposed to change the primary endpoint

of the ongoing induction phase of the trial "to elevate enhanced clinical response from the first key secondary endpoint to a co-primary endpoint…..Consequently, the Hochberg method instead of the closed sequential testing procedure will be employed to test the two primary endpoints, "enhanced clinical response" and "clinical remission". The meeting minutes reflect the following:

> **We do not recommend you change the definition of your primary endpoint while the study is underway. This may undermine the integrity of the trial, and will likely affect our interpretation of the statistical significance of the results. We recommend you continue the trial as planned, and we will evaluate the strength of your evidence based on both your primary and key secondary endpoints. These results can be used as supportive evidence along with your second study.**
>
> **The term co-primary endpoint that you have defined for Study C13007 is not commonly used for regulatory purposes.**
>
> **Two or more primary endpoints are called co-primary if each must show statistically significant treatment benefit at a pre-specified significance level α (e.g., α=0.025, by 1-sided tests).**
>
> ***Millennium provided clarification regarding the rationale for why they elevated a key secondary endpoint to a "co-primary endpoint" for the C13007 Induction Study. Their rationale included the following:***
>
> - ***In short term induction studies, it is more difficult to achieve remission in a more severe population.***
> - ***There is the realistic possibility of not achieving the remission endpoint for induction despite clinical benefit.***
> - ***The overall impact of a failed primary endpoint (i.e., "failed" trial) on the global program must be considered.***
> - ***Based on the previous plan with a sequential testing procedure, the "enhanced clinical response" endpoint cannot be tested if the "clinical remission" endpoint fails.***
> - ***In pivotal trials under the setting of hypothesis testing, pre-specification of endpoints and testing orders are critically important.***

In a July 13, 2010 meeting between the FDA and sponsor that primarily focused on the safety dataset requirements and design issues that pertained to risk of PML, the sponsor asked a question about the adequacy of the UC program (a single induction trial and a single maintenance trial). The FDA responded as follows:

> **In general, we strongly recommend two adequate and well controlled clinical trials. We refer you to "*Guidance for Industry- Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products.*" Because you are studying a new product for a new indication, we would require substantial evidence of efficacy demonstrated by strict control of the Type I error rate. We recommend your studywise Type I error rate be 0.001 or less (one-sided). We would need to see an effect size that is clinically relevant and meaningful. Additionally, this study should also meet the following requirements:**
>
> - **no single study/site provides an unusually large fraction of patients**

- **no single investigator or site provides a disproportionate favorable effect**
- **multiple endpoints involving different events**
- **statistically very persuasive findings**

In a July 24 and 25, 2012 Type C meeting between the FDA and sponsor, the FDA stated the following:

Although it appears that you have conducted two trials in CD, we cannot make a determination about whether the trials are adequate and well-controlled until we have reviewed the data.

Based on the information you have provided in the meeting package, it appears that efficacy for induction in CD has not been demonstrated (see below):

- **Study C13007: It appears that there were two co-primary efficacy endpoints, and only one of the two co-primary endpoints was met.**
- **Study 13011: It appears that the primary efficacy endpoint was not met. See also Additional Comment 24.**

We cannot be certain at this time that the results of the maintenance trial will constitute substantial evidence of efficacy for maintenance in CD.

The same comments in the Response to 1a regarding demonstration of efficacy for induction in UC also apply to demonstration of efficacy for maintenance in CD.

We also note the following:

- **As we stated in the June 5, 2008 meeting[3], "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." Thus, it may not be possible for you to demonstrate efficacy for maintenance in CD if efficacy for induction in CD has not been demonstrated.**
- **It appears that your maintenance study was designed so that patients from two different cohorts (Cohort 1 and Cohort 2) enter into the maintenance study. We note that you have only presented the results of a combined analysis. We request that you provide a separate analysis for each of the cohorts for your primary and secondary endpoints of the maintenance study.**

It is premature to discuss the specific wording of the indication statement. Such discussions will occur after results of the appropriate studies have been reviewed, and it is determined that the studies have each met the primary endpoint and other relevant endpoints.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) is currently re-evaluating endpoint definitions in CD and UC. DGIEP is also currently re- evaluating the requirements to support labeling claims for "mucosal healing" in UC (i.e., definition, standardized endoscopy methodology,

use of histology, etc.). This process includes internal discussions as well as workshops that include external experts; FDA is currently planning an Inflammatory Bowel Disease (IBD) Workshop in Fall 2012 in which many of these topics are likely to be discussed.

3. CMC

I concur with the conclusions reached by the Quality reviewers, including the Microbiology Quality reviewers, regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The Quality reviewers have recommended approval, with a number of PMCs. These PMCs relate to development of improved assays for setting drug substance and drug product acceptance criteria, lot release, as well as development of testing for osmolality and polysorbhate 80 levels for controls for release of drug product. In addition there is a PMC to provide supplemental data to support monoclonality of the cell line. The Microbiology Quality Drug Substance reviewers have recommended approval with PMCs to further evaluate endotoxin testing procedures for the drug substance and the (b) (4) The Microbiology Quality Drug Product reviewers have recommended approval with PMCs to further perform further studies for container closure integrity, and validation of endotoxin assays for the drug product (b) (4) See Section 5 Clinical Pharmacology for discussion of recommendations for PMCs to address improving assays to detect anti-drug antibodies.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with their recommendation for a PMR under PREA to require juvenile animal data before proceeding with pediatric trials. Their labeling review recommendations were incorporated in labeling negotiations with the applicant. The Pharmacology/Toxicology reviewers worked with the Maternal Health Team (from Pediatric and Maternal Health Staff) to develop labeling recommendations for Section 8.1 Pregnancy and Section 8.3 Nursing Mothers.

The Pharmacology/Toxicology reviewers evaluated the nonclinical data submitted by the applicant to support the selectivity of the monoclonal antibody and the potential for vedolizumab to have a decreased risk for adverse reactions of PML relative to other anti-integrin inhibitors. These nonclinical data included results from an experimental autoimmune encephalomyelitis (EAE) model in Rhesus monkeys, which is an animal model for multiple sclerosis (MS). Vedolizumab didn't appear to inhibit immune surveillance of the CNS in this model, whereas natalizumab did. The reviewers stated that these results "do not directly demonstrate that [vedolizumab] has no potential to cause PML."

Chronic toxicology data were submitted for two species, rabbit and Cynomologus monkeys. Minimal to mild splenic lymphoid hyperplasia in the periarteriolar lymphoid sheaths

and hyperplasia of submucosal lymphoid nodules in the ileum were observed in rabbits. No dose relationship was observed and these changes were also seen in control animals. For this reason the reviewers concluded "the relation to the treatment is uncertain." In monkeys, minimal to mild lymphoid depletion in the Peyer's patches of the gastrointestinal tract was observed in males at 10, 30, and 100 mg/kg/day, and increased gastric epithelial regeneration was observed in both sexes, associated with lymphoplasmacytic gastritis at 10, 30, and 100 mg/kg. Vedolizumab exposed monkeys had increased severity of regeneration of superficial mucosal epithelium in response to lymphoplasmacytic gastritis (lymphoplasmacytic infiltrates into the lamina propria of the stomach), which is a common incidental finding in Cynomolgus monkeys. Epithelial regeneration is an expected physiologic response to lymphoplasmacytic gastritis. The incidence of both the lymphoplasmacytic gastritis and the regeneration was similar between treated animals and controls; however, the severity of the epithelial response to the inflammation "was slightly increased in MLN0002 treated monkeys when compared to control monkeys. The toxicological significance of this increase in the regenerative response of the epithelium is not clear." Presence of Balantidium coli parasites were noted in the colons of both the treated and control monkeys. The reviewers noted that Balantidium coli are "common commensal intestinal parasites of macaques and are generally non-pathogenic" and "did not appear to be treatment related due to lack of a dose response, presence of this parasite in both controls and treated animals and reported background incidences."

Conventional carcinogenicity studies were not conducted as vedolizumab "lacks pharmacological activity in mice and rats." The reviewers noted that the lymphoid hyperplasia noted in the chronic dosing studies in monkeys and rabbits appeared to be from the immunogenicity (i.e., antigenic stimulation) associated with infusing these nonhuman species with a humanized monoclonal antibody.

5. Clinical Pharmacology

I concur with the conclusions reached by the Clinical Pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. I concur with the recommendation from both the Clinical Pharmacology reviewers and the Quality reviewers for a PMC to develop and qualify an anti-drug antibody (ADA) assay that tolerates therapeutic vedolizumab concentrations. This is based on inadequacy of the current assay for detecting ADA in the presence of the vedolizumab at steady state trough concentration, which is approximately 11 micrograms/ML. The current assay's drug tolerance level is 500 ng/mL, which is a 20 fold lower than the steady state trough concentration associated with the dosing regimen that will be approved. The rates of ADA reported by the applicant in this BLA were considered to be underestimated. In addition, the reviewers found evidence that the presence of ADA negatively impacted efficacy and substantially decreased serum concentrations of vedolizumab to undetectable or negligible. In the 8 patients that did have persistent presence of ADA identified, none achieved remission at either Week 6 or Week 52. I also concur with their recommendation for a PMC to reanalyze banked immunogenicity serum samples from the major UC and CD efficacy trials supporting this BLA, once the improved assay is available. This should ultimately result in an improved description of the incidence of ADA

with vedolizumab treatment and provide a foundation for better understanding the impact of ADA on pharmacokinetics and efficacy.

The reviewers have also recommended a PMC for the applicant to explore the indirect effects of vedolizumab on CYP enzymes, through the drugs impact on inflammation. This is based on current knowledge that cytokines associated with inflammatory conditions impact CYP expression. Changes in inflammatory conditions, as would be expected to occur with response to IBD treatments, could then change CYP expression, impacting metabolism of other medications taken concomitantly. I support this recommendation.

The drug product studied at various stages of development was produced with varying manufacturing processes, referred to as Process A, Process B and Process C. The Clinical Pharmacology reviewers note that Process C was used in the phase 3 trials and is the same as that which will be commercialized.

Some additional key Clinical Pharmacology review findings include:

1) Vedolizumab exhibits target-mediated drug disposition. As concentrations increase, the target saturates, and clearance decreases.

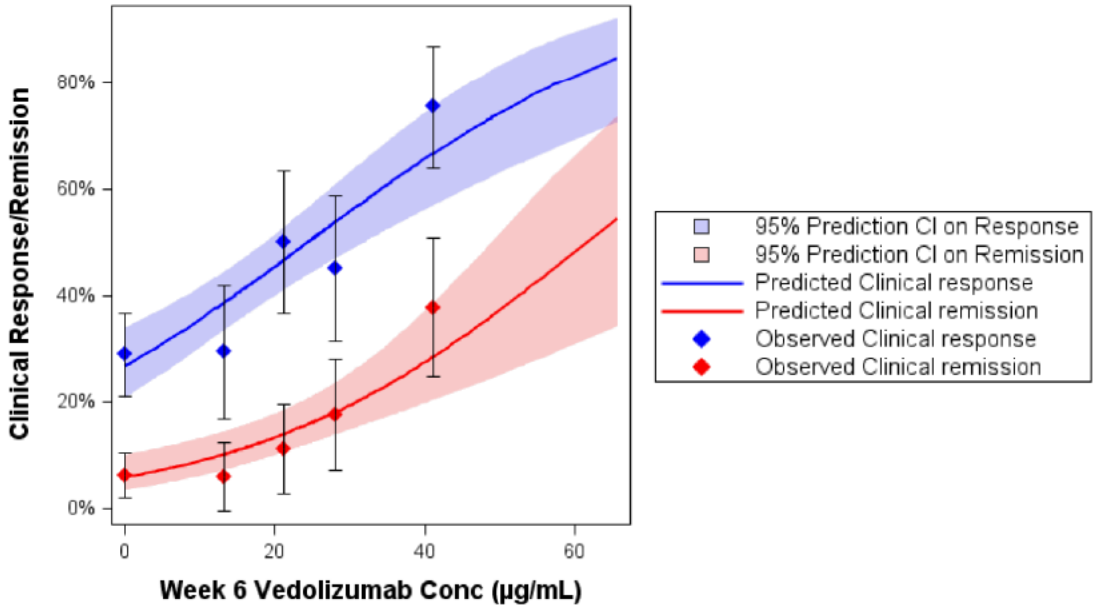
2) There were no apparent PK differences between patients with UC and patients with CD, based on Week 6 trough concentrations and steady state concentrations obtained during the "maintenance" phase.

3) Population PK analyses revealed no meaningful impact from disease severity, body weight, serum albumin, prior treatment with TNF alpha antagonists, age and co-administered medications on vedolizumab pharmacokinetics.

4) α4β7 binding saturation studies that evaluated serum inhibition of MAdCAM-1-Fc binding to α4β7 revealed that maximum (100%) α4β7 binding saturation was achieved within an hour after the first dose, at all doses over a range of 2-10 mg/kg. (The dose that will be approved is approximately 4 mg/kg, based on a 70 kg person). This level of inhibition was sustained for a substantial period of time: 84, 126 and 112 days for 2 mg/kg, 6 mg/kg and 10 mg/kg dose cohorts, respectively. The serum concentration associated with dropping below 100% ranged 2-6 micrograms/mL. Based on this, a Q 8 week dosing schedule (Q 56 days) would be expected to result in sustained maximum binding of vedolizumab to α4β7.

5) A significant exposure response relationship was observed for both clinical response and remission during the induction phase in UC. (See Figure 1 below, which is reproduced from the Clinical Pharmacology review.)

Figure 1 Exposure-Response Relationships for Clinical Response and Remission at Week 6 with Week 6 Vedolizumab Trough Concentrations



For the maintenance phase, there was no dose response observed between the Q 4 week and Q 8 week regimens, and no exposure response relationship was observed for Week 52 clinical remission. Multivariate logistic regression analyses were performed to make sure that imbalances in important potential confounders were accounted for, and the conclusions remained unchanged. The reviewers concluded that the Q 8week regimen should be approved. While the clinical trial data supported the efficacy of the 300 mg dose studied, in light of the exposure-response data from the induction phase, the reviewers recommended that the sponsor should explore higher doses in the induction phase during post marketing development to potentially further increase the responder rate.

6. No exposure-response relationship was identified in Crohn's Disease, for either enhanced clinical response or remission. Multivariate logistic regression analyses were performed to make sure that imbalances in important potential confounders were accounted for, and the conclusions remained unchanged. Exposure response analyses supported labeling the Q 8 Week dosing regimen (b) (4) for CD.

7. The reviewers evaluated exploratory analyses submitted by the applicant to support including a recommendation in the label to (b) (4) The reviewers concluded that these analyses did not support this recommendation because the data were limited (sample size low) and the analyses were not controlled and randomized (no control arm).

8. The reviewers evaluated the results of the applicant's exploratory analyses submitted to support a Week 14 time point for decisions regarding continuation of treatment with vedolizumab. The applicant stated that these analyses indicate that nonresponders at Week 6 may achieve response by Week 14 in both UC and CD. In addition, these analyses suggest that persistent non-response by Week 14 and loss of response by Week 14 are indicators of futility of continued vedolizumab treatment. The Clinical Pharmacology reviewers supported inclusion of the information in the label that if a patient has not responded by Week 14, treatment should be discontinued. (Section 2.3 Dosage in Adults with Ulcerative Colitis or Crohn's Disease of the product label will include the statement, "Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14".)

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

DGIEP generally recommends that sponsors conduct at least two trials to support an induction indication. However, highly persuasive findings from single induction trial with the characteristics described in the Guidance to Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products can support approval of an induction indication. Success in the induction trials can be used to support the efficacy findings from a single maintenance trial.

Sponsors have generally followed precedents of previously approved products as guides for the indications they seek and as guides for the clinical development programs they pursue to support those indications. However, in recent years DGIEP has been reevaluating its regulatory approach to drug development in IBD. For example, DGIEP has evaluated whether the IBD trial designs traditionally used to support NDA/BLA submissions yield data that support the actual wording of indication statements that sponsors/applicants seek. The Division now recommends that for a "maintenance of remission" indication, the trial should be designed to show that patients who have achieved remission during induction, remain in remission over time. (Previous approaches allowed for this indication if patients who had achieved clinical response with induction had subsequently achieved remission by the time of completion of the maintenance trial.) In addition, the Statistical reviewers have pointed out that re-randomization after induction is necessary to validly evaluate "maintenance". For this reason, if re-randomization was not performed at entry into the maintenance trial, the Division has begun to refer to the continuation of remission in the indication statement as "sustained" remission instead of "maintenance" of remission. In addition, the Division has moved away from describing endoscopic remission (as defined by Mayo endoscopic subscore in UC) as

"mucosal healing" because this score describes the mucosal visual appearance, and does not incorporate a histological evaluation. The Division has replaced "mucosal healing" with "improvement in endoscopic appearance."

The following table, reproduced from the CDTL review, summarizes the phase 3 trials that were conducted to support the components of the UC and CD indications the applicant seeks. There was a single trial conducted to support induction and maintenance in UC. The primary endpoints for the induction trials in both diseases include Clinical Response. Patients could be randomized into the maintenance trials in both diseases if they had achieved at least a Clinical Response during induction treatment. The primary endpoint for the maintenance trials is remission at a single time point, Week 52. Although the primary endpoint of the maintenance trials is not remission at Week 52 *in patients who were in remission at baseline*, the maintenance trials in both indications included a secondary endpoint that evaluated the efficacy outcome in the population that entered the trials in remission at baseline.

Table 1. 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

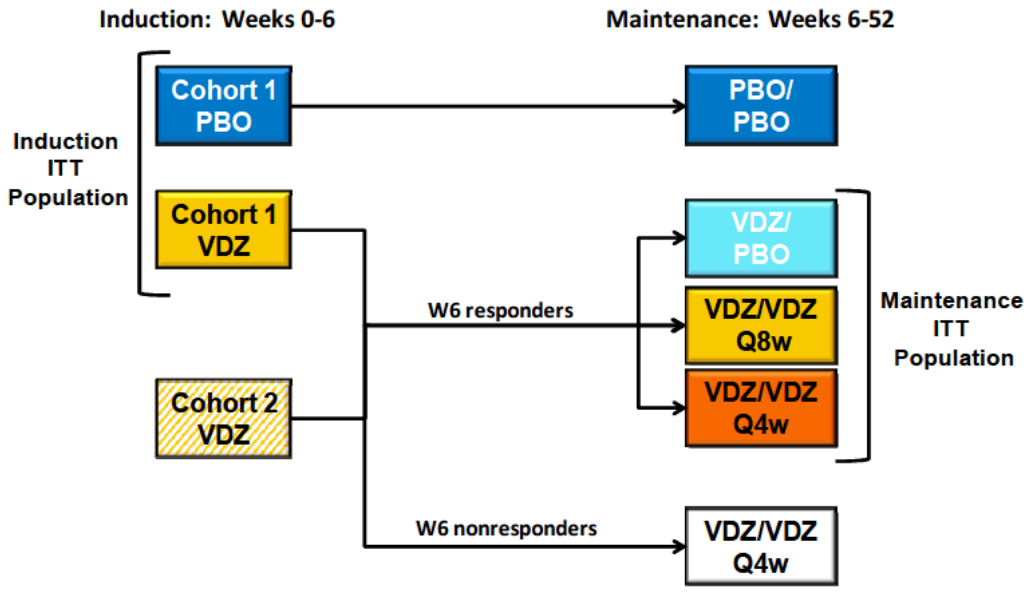
PBO: Placebo; VDZ: Vedolizumab; *ITT
[#] For each Maintenance Trial (C13006 and C13007), patients must have achieved Clinical Response at Wk 6 in the corresponding Induction Phase (see UC and CD Clinical Reviews for details)
[†]Alternative endpoints: at least one of the two alternative primary endpoints 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.

The trials included in the CD and UC programs were similar in design. In both programs patients were re-randomized if they had achieved at least a clinical response, for entry into the maintenance trial. An open label induction cohort was enrolled and treated to supplement

enrollment into the maintenance trials. From both an efficacy and safety standpoint, the population enrolled in these trials was a key review issue. As described earlier in my review, the concerns regarding potential risk for PML associated with vedolizumab because of its integrin targeting, prompted the FDA reviewers to require that U.S. subjects have had an inadequate response or intolerance to immunomodulator therapy such as azathioprine or 6-MP and/or inadequate response, loss of response or intolerance to a TNF alpha antagonist. This was not the case outside the US, where prior treatment limited to only corticosteroids was sufficient for qualifying for entry. (Patients had to be corticosteroid dependent or had an inadequate response or intolerance to corticosteroids). In addition, US patients who entered the trial on immunomodulators, had to have these drugs discontinued at the end of induction (duration of concomitant use was limited due to safety concerns).

Both the UC and CD programs included two Cohorts in the induction phase. Cohort 1 was randomized to compare treatment with vedolizumab to placebo for induction claims. Cohort 2 was sequentially enrolled after completion of accrual to Cohort 1, and all patients in Cohort 2 were treated with open label vedolizumab in order to identify Week 6 clinical responders who would be eligible for randomization into the maintenance phase trial. The following figure for the UC program, which is reproduced from Takeda's AC briefing document, provides an overview of how the cohorts contributed to the efficacy evaluation in the maintenance phase.

Figure 7-1 Study Design for Induction and Maintenance (UC Study C13006)



Abbreviations: ITT = intent-to-treat; PBO = placebo; Q4w = every 4 weeks; Q8w = every 8 weeks; UC = ulcerative colitis; VDZ = vedolizumab; W6 = Week 6.

In addition, the figure points to the prospective plan to explore response to open label Q 4 week vedolizumab dosing in patients who had not responded to vedolizumab by Week 6. This plan was a part of both the UC and CD programs, and included open label assessments of clinical response. (For the blinded components of these trials, an unblinded site pharmacist provided drug to blinded site personnel in masked infusion bags based on treatment

assignment from an IVRS system.) The applicant presented clinical response data from these patients at Week 10 and Week 14, which suggested nonresponders at Week 6 who continued treatment with vedolizumab with doses at Week 6 and Week 10, may subsequently demonstrate a response by Week 14. This exploratory analysis raised questions regarding whether the efficacy assessment for induction may have been performed too early, particularly in the CD trials.

Ulcerative Colitis. The single induction and single maintenance trial for UC both met their prespecified primary endpoints and key secondary endpoints, and the results were statistically very persuasive. The Mayo Score was used to assess efficacy. The endpoints are summarized in the tables below, which are reproduced from the CDTL review.

Table 2. 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).

Table 3. 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.

The reviewers agreed that the efficacy results support approval of vedolizumab 300 mg at zero, two and six weeks, followed by every 8 weeks for the applicant's proposed indications; however, instead of describing the endoscopic results as "mucosal healing" the reviewers recommended that the findings be described as "improvement in mucosal appearance", which is consistent with the wording that has be utilized for more recently approved products. The secondary endpoint analysis in the maintenance trial for durable clinical remission was statistically significant, which supported a maintenance of remission indication. As discussed in Section 5 Clinical Pharmacology of my review, there is no evidence that the Q4 week regimen provides superior results to the Q8 week regimen. The efficacy results summarized below are reproduced from the CDTL review.

Table 4. 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

Table 5. 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

Exploratory subgroup analyses comparing outcomes in the subgroup of patients who had no prior exposure to TNFα antagonists vs. those who had inadequate response/loss of response or intolerance to TNFα antagonists demonstrated numerically higher results for the no prior use subgroup in the induction phase, but similar results between groups during maintenance. A subgroup analysis that evaluated patients who met US protocol criteria vs. those who did not suggested numerically higher remission and response rates in the induction phase among patients who did not meet US entry criteria; however, results were numerically similar between the two groups for the outcomes in maintenance.

The majority of the Advisory Committee panelists agreed that the benefit-risk assessment supported approval of vedolizumab for UC in the overall population studied in the UC trials, i.e., not restricted to the population studied based on the US entry criteria. The pertinent AC meeting questions and votes are shown below:

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 Summary: A=13; B=8; C=0

Crohn's Disease. Although the IND sponsor conducted two induction trials to support the Crohn's disease indication, the trials differed in the study populations that were enrolled. Study C13007enrolled a population with prior treatment exposure similar to the UC induction trial (US sites enrolled patients with inadequate response or intolerance to immunomodulatory therapy with azathioprine, 6-MP or methotrexate and/or inadequate response, loss or response, or intolerance to one or more TNF α antagonists, whereas the ex-US sites allowed entry of patients who were merely corticosteroid dependent or had an inadequate response or intolerance to corticosteroids). In Study C13007 there was a prospective plan to limit enrollment of patients with prior TNF α antagonist exposure to **half** of the total study population. However, in the other CD induction trial, Study C13011, the prespecified primary efficacy analysis population was patients in whom TNF α antagonists had failed, and this trial specified that **approximately 75%** of patients were to have failed previous TNF α antagonist therapy. Patients who had failed only corticosteroids or immunomodulators were allowed to enter the trial; however, randomization was stratified and the TNF α antagonist failure population was preferentially targeted for enrollment in order to achieve the sample size needed for the primary efficacy analysis. In both induction trials, immunomodulators had to be discontinued in the US patients at the end of induction (duration of concomitant use limited due to safety concerns). The tables below summarize the endpoints in the CD trials.

Table 6. 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)

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

As summarized in the tables below (reproduced from the CDTL review), the primary efficacy analysis of clinical remission at Week 6 in patients who were TNF α antagonist failures failed to reach statistical significance in Study C13011. The primary analysis in C13007, clinical remission at Week 6, favored vedolizumab, but was not highly statistically persuasive. The analysis of the first key secondary endpoint failed in C13007. The Clinical reviewer expressed concern that the lack of statistically significant impact on this biomarker might reflect inadequate impact of vedolizumab on inflammation in CD.

Table 8. 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)	0.041*	**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**	--

*adjusted p-value for multiple comparisons of two primary endpoints. (Clinical Remission or CDAI 100 Response)
Source: Pages 136 and 140 of the C13007 Study Report

Table 9. 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

An exploratory analysis of the overall population of C13011 (not limited to the prespecified efficacy analysis population in whom TNF α antagonists had failed) suggested a favorable effect of vedolizumab; however, this analysis could not be considered a statistically valid result, in light of the failed prespecified primary analysis. (A Week 6 and Week 10 analysis of the overall population were secondary endpoints, but formal hypothesis testing was precluded by the failure to achieve statistical significance on the prespecified primary efficacy analysis.) The observed outcomes from an additional prespecified secondary endpoint, analysis of Week 10 efficacy in the TNF α antagonist failure population, was of interest, in light of apparent "delayed" onset of efficacy in this population, but again formal hypothesis testing was precluded by the statistical analysis plan. See discussion of the observed results from this exploratory analysis later in this review.

The results of the "maintenance" trial portion of Study C10007 provide some support for vedolizumab's ability to bring about a clinical remission in patients with CD over time. The endpoints for the "maintenance" trial are summarized below, followed by the efficacy results (tables reproduced from the CDTL review).

Table 10. 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

Table 11. 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

Results demonstrate superiority in Clinical Remission at Week 52 among patients who were randomized to vedolizumab after achieving a minimum of a Clinical Response by Week 6 of induction treatment. However, analysis of Durable Clinical Remission, in which Clinical Remission was present for at least 80% of study visits, including Week 52, was not statistically significant. For this reason the maintenance of remission indication was not supported by the data. The applicant argued that if the analysis was limited to a comparison of proportion of patients in remission at just two time points (i.e., Week 6 and Week 52), as was done for the durable remission secondary endpoint analysis for UC, then vedolizumab appears superior to placebo. However, this analysis was not prespecified in CD, and given that the Durable Clinical Remission analysis failed to achieve statistical significance, no valid conclusions could be drawn from further analyses. In addition, remission for UC is defined in part by endoscopy, which was only performed at two time points in the UC trial; whereas the CDAI

defined remission in the CD trials and was to be performed at each followup visit, i.e., every 4 weeks.

There were additional concerns about the adequacy of the data to support the Crohn's disease indication expressed by the primary Statistical reviewer. His review describes concerns about the strength of evidence submitted to support the maintenance indication: 1) differences between the two induction cohorts from which responders entered the maintenance trial, coupled with differences in treatment effect observed between these cohorts within the maintenance trial, and 2) high missing data rate during the maintenance trial. He performed exploratory sensitivity analyses that he believed provided evidence that the observed efficacy outcomes were not robust. The secondary Statistical reviewer acknowledged those concerns; however, she pointed out that observed differences aren't completely unexpected, given the larger number of patients from Cohort 2 of C13007 that contributed to the maintenance trial (relative to Cohort 1) and the targeted enrollment of a specific proportion (no more than 50%) of patients that had prior exposure to TNFα antagonists in Cohort 1, whereas Cohort 2 was not so limited. With regard to the missing data, the Secondary reviewer noted that across treatment groups, the majority discontinued due to adverse event or lack of efficacy, and that such a pattern of missing data would be expected in this difficult to treat disease in a study of such a long duration. She cautioned against placing too much reliance on exploratory subgroup analyses and exploratory sensitivity analyses. She concluded:

> "The subgroup analyses showed an expected variability of the treatment effect. The statistical significance stated by the primary reviewer, including the discussion on the 95% CI coverage, for all these analyses should be viewed with caution due to their exploratory nature, and focus should be on the descriptive statistics.
>
> *Conclusion*
>
> In summary, Study C13007 showed statistically significant benefit of vedolizumab compared to placebo for treatment of CD, as demonstrated by one of the Induction primary efficacy endpoints, the Maintenance primary efficacy endpoint and two of the three Maintenance secondary efficacy endpoints. However, treatment effect sizes observed were relatively small and an induction period longer than six weeks may be needed for some patients to achieve clinical response."

The Advisory Committee was asked to vote on the adequacy of the data to support the CD indications. The pertinent Questions and votes are summarized below:

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: 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.

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

However, the single member who had originally voted "No" subsequently noted during the explanation of the vote that she wanted to vote "Yes."

Although the majority of the Advisory Committee voted in support of both CD induction and maintenance indications, the data analyses do not clearly support their vote, particularly their overwhelming conclusion that the data supported a maintenance claim, in the context of their less unanimous conclusion that the data supported an induction claim. The Committee vote suggests that their decision was not based on the DGIEP's regulatory framework for defining a maintenance indication. Clearly, the Committee viewed the combined data from the induction and maintenance settings as substantial evidence that vedolizumab will provide clinical benefit to patients over the course of time. The Clinical Reviewers concluded that the body of evidence indicated that vedolizumab treatment is associated with clinical benefit in patients with CD; however, the benefit shown in the trials could not be readily described in the traditional paradigm. The CD indication will state that vedolizumab is indicated for achieving clinical response, clinical remission and corticosteroid-free remission. (b) (4)

The review of these trials highlighted two key concepts regarding operationalizing evaluation of the "induction/maintenance" paradigm in Crohn's disease trials. One was the importance of carefully considering how interim assessments of clinical symptoms during maintenance trials are incorporated into a definition of continuous remission. A prospective plan for interpreting those periods of apparent deterioration must be in place at the initiation of the trial. In this BLA, the IND sponsor had prespecified that if the number of assessments that no longer met criteria for remission consisted of <20% of the scheduled assessments, then the apparent deterioration would not be considered clinically relevant. If endoscopic evaluation is added to future CD trials in order to assess mucosal appearance as an indicator of a drug's impact on the inflammatory process, then the analysis plan for incorporating the interim clinical symptom assessments (between endoscopies) must be addressed. In the UC trial submitted in this BLA, even though serial partial Mayo scores were obtained on interim visits, the remission analyses were based only on the complete Mayo score (when endoscopic score was available).

An additional issue exemplified by the data in this application is the need to define, based on evidence obtained during early phase trials, when it is most likely that onset of remission or meaningful clinical response will occur, so that induction will be assessed when most of the patients would be expected to have achieved the desired clinical results, and the maintenance phase trials could begin when most of the patients would have been expected to have achieved

those results. The applicant pointed to trial data that suggested that CD patients may need longer than 6 weeks to achieve a meaningful clinical response to treatment, and that the strength of evidence to support vedolizumab's ability to induce remission may have been greater if the efficacy assessment had occurred later than 6 weeks, e.g., 10 weeks. (Patients treated with vedolizumab in Study C13007 who did not achieve response to induction treatment at Week 6, were retained in the study to explore response after a Week 6 dose, and are referred to in the Clinical Review as non-intent to treat maintenance study patients.) As per the quotation from the Statistical reviewer above, the secondary Statistical reviewer agreed that the exploratory analyses presented by the applicant suggest that this might be true. The primary Clinical reviewer concurred.

Subgroup analyses were performed that compared efficacy results between CD patients with no prior use of TNFα antagonists vs. those who had a history of inadequate response, loss of response or intolerance. In the induction study C13007, there was little difference between groups at Week 6; whereas for the maintenance component of Study C13007, there was a numerically higher remission rate and CDAI-100 response rate at Week 52 in patients who had no prior use of TNF alpha antagonists. The opposite trend was observed for Corticosteroid-free Clinical Remission. Subgroup analyses based on whether patients met US entry criteria vs. the ex-US criteria suggested little difference between groups in the Induction component of Study C13007; whereas for the Maintenance component of Study 13007, the patients who met the less stringent ex-US entry criteria had numerically higher Week 52 Clinical Remission, Week 52 CDAI-100 Response and Corticosteroid-free Clinical remission rates. The Advisory Committee was asked whether the indications should be restricted to a specific population (consistent with the US site entry criteria vs. the overall trial entry criteria), and the Committee voted in support of not limiting the indication to the US study site entry criteria.

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

Summary. The Clinical reviewers have recommended approval of vedolizumab for both UC and CD. The Secondary Statistical reviewer concluded that "statistically significant benefit of vedolizumab compared to placebo" was shown for both UC and CD. The primary statistical reviewer's UC review appears relatively supportive of approval; however, in his CD review he seems less convinced that the data support approval of vedolizumab for CD. I concur with the

recommendation of the Clinical reviewers and the Secondary Statistical reviewer. The following indications will be included in product labeling:

1.1 Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

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

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

1.2 Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

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

The approved dose for both diseases will be:

2.3 Dosage in Adults with Ulcerative Colitis or Crohn's Disease

The recommended dosage of ENTYVIO in adults with ulcerative colitis or Crohn's disease is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

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

8. Safety

As described above, in Sections 1 and 2 of this review, defining the size and duration of exposure of an adequate safety dataset for BLA submission was a key point of pre-submission meetings between the FDA and the sponsor/applicant. The following table summarizes the exposure data for the BLA at the time of submission, based on a data cut off of June 27, 2013, and expressed as both number of infusions and time. As can be seen, data from just over a 1000 patients with at least 24 infusions were submitted.

Table12. 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

No cases of PML were identified. The sponsor had a prospective program to systematically identify cases of PML. An independent adjudication committee was involved in evaluation.

The CDTL summarized how these safety data informed FDA's evaluation of the risk of PML associated with vedolizumab as follows:

> "Using the "Rule of Three,"[1] 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 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)."

Regarding infections in general, not limited to PML, the CDTL review states:

[1] 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).

> "…..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."

There were 12 deaths in patients exposed to vedolizumab and none were attributed to study exposure to vedolizumab.

The Advisory Committee was asked the following questions regarding characterization of the risk of PML associated with vedolizumab (a key component of risk/benefit evaluation for a decision to approve), the potential for increased risk of PML with concomitant administration of immunosuppressants (a key issue for labeling) and the risk mitigation strategies (post-marketing considerations):

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**:** Members noted that continued monitoring and observation are still necessary to assess the potential risk of PML and the occurrence of serious infections.

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 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.

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: Committee members commented on the importance of quantifying PML risk and of monitoring for other infections. They noted that post-market risk mitigation strategies should not be burdensome.

Additional Safety Considerations:

Hypersensitivity. Cases of urticaria were identified, in addition to one case of anaphylaxis. The reviewers noted that 4% of patients who received vedolizumab experienced infusion reactions.

Hepatoxicity. Dr. Avigan from OSE prepared a consult regarding a potential hepatotoxicity signal identified in the review of the clinical safety database by Dr. Muldowney. Dr. Avigan noted: "There were several cases of acute hepatocellular injury during the vedolizumab clinical development program. Specifically, 4 patients reported serious adverse events of hepatitis during the controlled and open-label extension study. These adverse events occurred after a range of vedolizumab exposure, from 2 to 35 doses. All of these patients discontinued study drug and were treated with corticosteroids, and all recovered." He considered one of the cases "probably related to" vedolizumab treatment. He noted that there is mechanistic plausibility for such reactions as "integrin antagonists have a potential to affect regulatory T-cells that should ordinarily prevent autoimmune organ injury." Similar cases have been described associated with exposure to natalizumab, and are described in its labeling.

Malignancy. The safety dataset was examined to evaluate whether there was evidence that vedolizumab was associated with increased risk of malignancy. No increased risk was identified; however, in light of experience with other immunosuppressive drugs used to treat IBD, the reviewers recognized that more patient exposures over time may be necessary to detect a signal for this risk.

QT effects. A QT study was conducted that evaluated a single dose of 600 mg vedolizumab. The QT-IRT consult reviewer noted that this dose level is expected to provide maximum steady state vedolizumab concentrations that might be predicted with the proposed 300 mg dose regimen. The upper bound of the 90% confidence interval for ΔΔQTcF (ms) was 10.6 with the Process C product that will be commercialized. This change in QTcF does not raise safety concerns regarding QT prolongation with this product.

Summary.

The Advisory Committee voted that the risk/benefit assessment of vedolizumab was favorable for both the UC and CD indications. The FDA reviewers met to discuss the AC recommendations and whether a REMS or other strategies were needed to assure that the benefits of vedolizumab outweighed its risks when it was approved for both populations. The reviewers met with the REMS Oversight Committee (ROC) to discuss the AC recommendations and the review team's conclusion that the BLA could be approved without a REMS. The reviewers based their recommendation on the following:

1. Zero cases of PML emerged in the clinical trials program.

2. Non-clinical evidence does not establish an association between vedolizumab and PML.

3. The risk of PML can be ruled out with reasonable certainty in light of the totality of the evidence. Specifically, the potential risk of PML can be capped at 2.8/1000 patients. Commensurate with this level of risk and the fact that this is a potential and not actual risk at the time of approval, the potential risk of PML will be listed in the Warnings & Precautions section of the label, not in the boxed warning section of the label. Typically, ETASU REMS are not warranted unless the relevant risk to be managed rises to the level of a boxed warning. Although the utility of comparisons with Tysabri are limited, it is important to acknowledge that the risk of PML associated with vedolizumab can be capped within the lower end of the range of the risk of PML associated with Tysabri, <1 – 11/1000, depending on the presence of the identified risk factors. Also, the risk of 2.8/1000 is generally comparable to the current level of risk of PML associated with Tysabri based on premarket and postmarket data.

4. The potential unintended adverse consequences of requiring an ETASU REMS is an important consideration. An ETASU REMS may substantially reduce initial prescribing and drug utilization after approval and thus may cause moderate to severe UC and CD patients to experience an ongoing unmet medical need. Even if an ETASU REMS program were scaled back, the adverse impact of the REMS on utilization may be irreversible.

5. Enhanced pharmacovigilance will be required to ensure that maximal data on any PML cases, in addition to other cases of interest, is obtained at the time of initial reporting for each reported case.

6. A postmarket observational study will be required to further characterize the potential risk of PML and assess the serious risks of infections, and malignancies.

7. The number of patients studied by the Applicant is consistent with the 2011 Closed AC's determination of the number of patients and duration of time needed to adequately characterize the potential risk of PML in the premarket setting. Further, the 2013 AC agreed that the sponsor has adequately characterized the potential risk of PML before

approval. In light of this, it is suboptimal to require more patients to be studied for longer to assess the potential risk of PML before drug approval.

8. The Applicant will include the potential risk of PML in the drug labeling, may provide additional non-REMS related materials to health care professionals, similar to other sponsors and drugs, and has proposed a non-REMS Medication Guide as part of the vedolizumab labeling. The use of communication tools such as letters could be confusing to health care professionals if FDA has determined that the evidence does not support an association PML with vedolizumab, despite the inability to completely rule out the risk (i.e., the risk does not warrant a boxed warning).

The ROC concurred. The product label will include sub-section in Section 5 Warnings and Precautions to discuss the risk of PML. This subsection will state the following:

> Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.
>
> In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.
>
> Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

The product label will also include warnings in Section 5 Warnings and Precautions for: infusion-related reactions and hypersensitivity reactions, infections, liver injury and live and oral vaccines.

The Medication Guide will state that vedolizumab "may cause serious side effects", including PML. This risk is described for patients as follows:

> Although it has not been reported with ENTYVIO, it may be possible for a person to get progressive multifocal leukoencephalopathy (PML) (a rare, serious brain infection caused by a virus). People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any of the following symptoms: confusion or problems thinking, loss of balance, change in the way you walk or talk, decreased strength or weakness on one side of the body, blurred vision, or loss of vision.

The approval letter will include the following PMR study under 505(o):

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.

In addition, the ongoing extension study C13008, will be included in the approval letter as a PMC, as follows:

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

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.

Under "Reporting Requirements," the letter will also request the following reporting of specific adverse reactions of interest:

> 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.

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 BLA on December 9, 2013. Refer to the CDTL review for a detailed report of the questions posed to the Committee and the voting results. I have also described the voting results in individual sections of my review to describe how the vote impacted the ultimate FDA decisional process.

10. Pediatrics

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

For the CD indication, the PeRC agreed with a partial waiver in pediatric patients ages birth to less than 6 years because studies would be impossible or highly impractical. The PeRC agreed with a deferral in pediatric patients ages 6 to less than 17 years because adult studies have been completed and the product is ready for approval.

The PeRC agreed to a PREA requirement for juvenile toxicology study of 3 months duration to be conducted prior to initiation of the pediatric studies. See the approval letter for a list of the deferred pediatric studies that will be required under PREA.

The Maternal Health Team recommended a PMC under 506B to conduct a pregnancy exposure registry study in the U.S. that compares the pregnancy and fetal outcomes of women exposed to vedolizumab during pregnancy to an unexposed control population or to collect pregnancy exposure data by collaborating with an existing disease-based pregnancy registry. In addition, the Maternal Health Team recommended a PMC to conduct a milk-only lactation study in lactating women receiving vedolizumab therapeutically to assess concentrations of the drug in breast milk (to inform the Nursing Mother's subsection of labeling). These studies were incorporated in the Approval Letter.

11. Other Relevant Regulatory Issues

For both the UC and CD development programs, the Clinical reviewers noted in their reviews that a signed copy of FDA Form 3454 with an appended list of investigator names was submitted to the BLA. This certified that there was no financial arrangement with the clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

OSI inspected four clinical sites and ultimately concluded that the data generated by the sites could be used to support the respective indications. A 483 was issued at one site; however, the

OSI reviewers concluded that the violations noted at the site did not adversely affect data integrity or subject safety.

In addition, OSI inspected the IND sponsor regarding site monitoring and sponsor calculation of CDAI and Mayo scores. This was an important review issue because the sponsor calculated the scores centrally, and in their own monitoring had detected site errors in score calculations, which resulted in mis-categorization at the sites of responders/nonresponders. This impacted 59/895 subjects in UC Study 13006 and 107/1116 subjects in CD Study C13007. The Clinical and statistical reviewers determined that this issue did not impact evaluability of efficacy in these trials. The OSI reviewers noted that the sponsor took action and requested that the study monitor CRO improve review of the scores. The sponsor retrained the CRO and updated the monitoring plan. OSI concluded that the data from the trials could be used to support the respective indications.

12. Labeling

DMEPA and the Office of Prescription Drug Promotion (OPDP) concluded that the proprietary name of "Entyvio" was acceptable.

Key efficacy review issues were addressed in labeling negotiations with the applicant, with respect to wording of the Indications and Usage section of the product label. The applicant's proposal to refer to (b) (4) in the UC indication statement was not accepted. The wording was revised to be consistent with the Division's recent labeling for UC products that have succeeded in demonstrating endoscopic improvement, i.e., "improving the endoscopic appearance of the mucosa." In light of the concerns regarding the strength of evidence submitted to support an induction and maintenance claim in Crohn's disease, the FDA ultimately recommended describing the CD trial results as "achieving clinical response and clinical remission". The FDA did not accept the applicant's proposal for a CD indication of (b) (4).

In addition, from both an efficacy and safety review standpoint, the FDA accepted the applicant's proposal to not limit the indicated population to that studied at the US sites in the trial (as opposed to the ex-US sites). This was consistent with the recommendation of the majority of the AC Committee members who voted on this issue. Therefore, the vedolizumab will be indicated for CD and UC patients with moderately to severely active disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. (Patients who have only had an inadequate response with, were intolerant to or demonstrated dependence on corticosteroids will not be excluded.)

Only the Q 8 week dosing regimen (starting at Week 6, post Day 1 and Week 2 "induction doses") will be approved. The FDA did not agree to the applicant's proposal to (b) (4)

(b) (4) because there was inadequate evidence to support this recommendation. (b) (4)

(b) (4)

A non-REMS Medication Guide will be included in product labeling to inform patients of the potential risk of serious infections, including PML, and hepatic toxicity.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment – The reviewers, with the exception of the primary Statistical reviewer, have recommended approval of vedolizumab for treatment of both UC and CD, as delineated by the wording of the indication statement (see Section 7 of this review). The Advisory Committee recommended approval of vedolizumab for both diseases, and voted that they considered the risk/ benefit favorable in both disease settings. No cases of PML have been identified to date. The only reviewer who has registered concerns regarding the risk/benefit of vedolizumab was the primary Statistical reviewer, who expressed particular concern that the applicant might not have established substantial evidence of efficacy for treatment of Crohn's Disease. (His review states, "Evidence of efficacy given in Study C13007 might not be statistically persuasive.") His concerns and the secondary Statistical reviewer's response to those concerns are summarized in Section 7 of this review. I believe that the data in both the UC and CD programs established clinical benefit of vedolizumab and support the indications that will be included in product labeling. This product offers another treatment option for patients with inflammatory bowel disease. Based on the safety data available for review in this NDA, which included a substantial number of patients who had been received at least 24 infusions of vedolizumab, the benefit outweighs the potential risks associated with the product. A PMR study and "enhanced pharmacovigilance/reporting" will be utilized to further evaluate risk during the post-marketing period. Whether vedolizumab is an anti-integrin therapy that has less risk for causing PML than other anti-integrin products remains to be established.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – As described in this review, the clinical and nonclinical safety data from this BLA were presented to an Advisory Committee and to the REMS Oversight Committee. The Advisory Committee did not recommend restricted distribution or specific risk mitigation procedures. The review team recommended approval without a REMS, and the REMS Oversight Committee concurred. Safety issues will be managed with

labeling, a PMR observational study, and "enhanced pharmacovigilance" described under "**Required Reporting**" in the approval letter.

- Recommendation for other Postmarketing Requirements and Commitments

The PMR study required under 505(0) is described in Section 8 Safety of this review and can be found in the approval letter. PREA PMRs can be found in the approval letter. The applicant will be required to conduct deferred pediatric studies for UC and CD. A juvenile animal study will be required prior to initiating pediatric studies. Other PMCs related to pregnancy and lactation, product quality, and further assessing presence of anti-drug antibodies using an improved ADA assay format with reduced sensitivity to product interference can be found in the approval letter.

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/s/

DONNA J GRIEBEL
05/20/2014