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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director (acting) Decisional Memo

Date	May 19, 2014
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director (acting) Decisional Memo
NDA/BLA #	BLA 125476
Applicant Name	Takeda Pharmaceuticals U.S.A., Inc.
Date of Submission	June 20, 2013
PDUFA Goal Date	May 20, 2014 (Ulcerative colitis) June 18, 2014 (Crohn's disease)
Proprietary Name / Established (USAN) Name	Entyvio/vedolizumab for injection
Dosage Forms / Strength	Lyophilized powder for reconstitution/300 mg/vial in a 20 mL vial
Proposed Indication(s)	<p>1. Adult Ulcerative Colitis: 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.</p> <p>2. Adult Crohn's Disease: Indicated for achieving clinical response, achieving clinical remission, 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.</p>
Action:	Approval

Summary

Ulcerative colitis (UC) and Crohn's disease (CD) are forms of chronic inflammatory conditions of the gastrointestinal (GI) tract or inflammatory bowel disease (IBD). Both UC and CD share many common clinical manifestations including diarrhea, abdominal pain, fecal urgency, and incontinence. Fever, weight loss, and fatigue are indicators of more extensive disease. The exact cause of IBD is unknown; however, the etiology is likely a combination of genetic, environmental and infectious factors.

The estimated prevalence of UC in the U.S. is approximately 450,000 individuals. UC is more common in Caucasians and individuals of Jewish descent. UC is typically diagnosed in individuals between the ages of 15 and 30, but the age of onset can vary widely. The estimated prevalence of CD in the U.S. is approximately 620,000 individuals. CD affects men and women equally, and is more common in individuals of Jewish descent. CD is typically diagnosed between the ages of 13 and 30, but can occur at any age.

Available treatments for moderately to severely active UC include corticosteroids, immunomodulators, and monoclonal antibodies targeting tumor necrosis factor (TNF)- α (i.e., infliximab, adalimumab, and golimumab). Available treatments for moderately to severely active CD include corticosteroids, immunomodulators, TNF- α antagonists (i.e., infliximab, adalimumab, and certolizumab) and the integrin antagonist natalizumab (Tysabri). As many patients are unable to achieve sustained remission, or are intolerant to, or experience side effects from currently available treatment regimens, additional treatment options are needed.

The subject of this BLA, Entyvio (vedolizumab), is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to the $\alpha_4\beta_7$ integrin, a glycoprotein expressed on the surface of certain populations of leukocytes involved in GI mucosal immunity. The natural ligand for $\alpha_4\beta_7$ integrin is mucosal addressin cell adhesion molecule 1 (MAdCAM-1), which is expressed on vascular endothelial cells of the GI mucosa. Binding of $\alpha_4\beta_7$ integrin to MAdCAM-1 mediates migration of leukocytes into the GI mucosa and associated lymphoid tissue. Vedolizumab binding to $\alpha_4\beta_7$ integrin prevents the $\alpha_4\beta_7$ -MAdCAM-1 interaction, thus preventing the migration of leukocytes into the GI mucosa, and decreasing the inflammation associated with UC and CD.

This memo documents my concurrence with the Division of Gastroenterology and Inborn Error Products' (DGIEP) approval recommendation for Entyvio (vedolizumab) in the treatment of patients with UC and CD.

Dosing

Vedolizumab is available as a lyophilized powder (in 20 mL single dose vials) to be reconstituted with 4.8 mL sterile water and diluted in 250 mL of sterile 0.9% sodium chloride for intravenous infusion. The recommended dose of Entyvio in patients with UC or CD is 300 mg administered over 30 minutes at zero, two and six weeks and then every eight weeks thereafter.

The Office of Clinical Pharmacology (OCP) agrees that the proposed dosing regimen is appropriate, although notes that a significant exposure-response relationship for clinical response and remission was demonstrated only during the induction phase for UC, and not during the maintenance phase for UC or during the induction or maintenance phases for CD. No dose-response was evident between the Q4W and Q8W dosing regimens in either UC or CD patients. OCP opined that available evidence suggests a delay in achieving response in the induction phase in both UC and CD patients, and assessing clinical response at Week 6 may be too early and that Week 10 or 14 may be a more appropriate time to assess for response. OCP concurs with the applicant that UC and CD patients who are non-responders at Week 14 are unlikely to achieve additional benefit with continued dosing and discontinuation of therapy should be considered. OCP has also recommended that the applicant consider exploring the possibility of higher doses of vedolizumab in the induction phase for UC (post-approval) with the aim of achieving higher remission rates.

Due to the potential for anaphylaxis and hypersensitivity reactions, Entyvio should be administered by a healthcare professional prepared to manage such reactions, and in a setting that provides appropriate monitoring and medical support. A patient's immunization status should be brought up to date prior to the initiation of treatment with Entyvio.

Regulatory History

Clinical development of vedolizumab began in 1998, and IND 009125 was opened in June 2000 to initiate clinical development in the U.S. In January 2006, development of vedolizumab was placed on clinical hold due to concerns that integrin antagonists might predispose patients to progressive multifocal leukoencephalopathy (PML). The clinical hold was lifted in July 2007 at which time an active screening and monitoring program was implemented in all clinical trials.

A joint meeting of the Gastrointestinal Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee was held in July 2011, to seek recommendations regarding the Phase 3 trial design for vedolizumab, including the number of patients and duration of study needed to exclude an unacceptable risk of PML. Based on the committee's deliberations, various trial design features including patient selection criteria, patient screening and monitoring, the use of concomitant medications, and the size of the safety database prior to BLA submission were agreed to with the applicant.

Several formal meetings occurred between the applicant and FDA to discuss manufacturing changes.

Fourteen face-to-face meetings, numerous teleconferences and written correspondences between the applicant and FDA were conducted during the clinical development program.

In February 2013, Fast Track Designation was granted for vedolizumab in the treatment of UC and CD.

BLA 125476 was submitted on June 20, 2013. The ulcerative colitis indication was granted a priority review; however, a major amendment submitted December 6, 2013 resulted in an extension of the user fee goal date to May 20, 2014. The Crohn's disease indication was granted a standard review with a user fee goal date of June 18, 2014.

Product Quality Considerations

During product development, several manufacturing changes were implemented, resulting in three different iterations of the product. The impact of these changes was adequately assessed and supports the comparability of vedolizumab across the iterations.

The Division of Monoclonal Antibodies (DMA) concluded that the manufacture of vedolizumab is well-controlled and leads to a product that is pure and potent; that the product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA; and that the conditions used in manufacturing have been sufficiently validated and a consistent product has been manufactured from the multiple production runs. DMA has recommended that vedolizumab be approved for human use. DMA has further recommended an expiry period of 36 months for drug product when stored at 2-8°C, and an expiry period of (b) (4) months for drug substance when stored at (b) (4).

DMA evaluated the three assays used to evaluate the immunogenicity of vedolizumab. These included anti-drug antibody (ADA) detection, ADA confirmation and neutralizing ADA. DMA noted that the drug tolerance of the detection assay was lower than the free drug concentration expected to be present in patients' serum samples at steady state at the proposed dosing regimen. Therefore, the current immunogenicity assays are unlikely to provide an accurate measure of the immunogenicity of vedolizumab. The applicant will develop improved immunogenicity assays that are more sensitive and drug tolerant, as a post-approval commitment.

On December 12, 2013, DMA concurred with the applicant's request for a categorical exclusion from environmental assessment under 21 CFR 25.31(c).

The Office of Compliance, Division of Good Manufacturing Practice Assessment (OC-DGMPA) issued a waiver recommendation for inspection of the (b) (4) facility (b) (4) manufacturer of the drug product. This was because of recent inspections and correctional activities already being monitored by the (b) (4).

All other facilities involved in the manufacturing of vedolizumab were evaluated by OC-DGMPA. A final Therapeutics Biological Establishment Evaluation Request Form was issued by OC-DGMPA on May 2, 2014, which stated that there are no pending or ongoing compliance actions that prevent approval of this application.

The applicant has agreed to the following post-marketing commitments (PMC):

1. To perform additional testing to confirm the monoclonality of the master cell bank.
2. To add osmolality testing to the vedolizumab drug product lot release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.
3. To add polysorbate 80 testing to the vedolizumab drug product lot release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.
4. To develop a non-reducing SDS-based assay that is capable of providing quantitative data for the evaluation of size-related impurities and to implement this assay in the release and stability programs for vedolizumab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.
5. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to vedolizumab, including procedures for accurate detection of binding antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling.
6. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to vedolizumab, including procedures for accurate detection of neutralizing antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling.
7. To develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the vedolizumab drug substance release program. The analytical procedure, validation report, proposed

acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

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

Microbiology Product Quality Considerations

There are no microbiology product quality issues that preclude approval of vedolizumab. The drug substance section of the BLA was recommended for approval with the following PMCs:

1. To conduct a maximum hold time study for the formulated drug substance using representative containers. If low endotoxin recovery is found in the formulated drug substance during the maximum hold time study, either hold times will be reevaluated or an alternative method to measure endotoxin in formulated drug substance will be developed and validated.
2. To verify the endotoxin recovery results for the (b) (4) and establish action limits for this solution once the results are confirmed by a validated method. If low endotoxin recovery is found, maximum hold times (b) (4)

The drug product section of the BLA was recommended for approval with the following PMCs:

1. To assess the sensitivity of the current dye and microbial ingress assays for container closure integrity testing. The studies will be conducted by perforating the container closure system with needles and capillaries that vary in internal diameter down to an internal size of (b) (4). If it is determined that the current methods are not sensitive to perforations of (b) (4) the methods will be optimized as necessary for the detection of breaches (b) (4).
2. To conduct studies to qualify the endotoxin kinetic turbidometric LAL assay for testing vedolizumab bulk drug product and finished drug product. Qualification studies will be conducted on three lots of endotoxin-spiked undiluted bulk drug product and finished drug product held under worst case hold conditions in the relevant containers. These

studies should demonstrate acceptable endotoxin recoveries of spiked endotoxin initially and after worst case hold conditions. In the event kinetic turbidometric qualification studies demonstrate that acceptable endotoxin recoveries from the spiking studies are not achieved, the USP <151> rabbit pyrogen method will be used to release the finished drug product.

3. To conduct studies to qualify an endotoxin assay for Vedolizumab Drug Product

(b) (4) Validation will be conducted with (b) (4) held under worst case conditions in the relevant containers. The qualified methods will be implemented for routine testing of the drug product (b) (4)

Non-clinical Considerations

In vitro studies utilizing human and murine cell lines selectively expressing specific integrins demonstrated the specificity of vedolizumab for binding to the $\alpha_4\beta_7$ integrin and not $\alpha_4\beta_1$ or $\alpha_E\beta_7$. The selectivity of vedolizumab for inhibition of $\alpha_4\beta_7$ -mediated cell adhesion interactions was also examined and demonstrated that vedolizumab inhibited $\alpha_4\beta_7$ -MAdCAM-1 and $\alpha_4\beta_7$ -fibronectin and did not inhibit $\alpha_4\beta_7$ -VCAM-1, $\alpha_4\beta_1$ -VCAM-1, or $\alpha_4\beta_1$ -fibronectin-mediated adhesive interactions.

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

Conventional carcinogenicity studies were not conducted with vedolizumab to assess its carcinogenic potential as it lacks pharmacological activity in mice and rats. However, the carcinogenic potential was assessed in an *in vitro* study using human tumor cells that expressed $\alpha_4\beta_7$ integrin; there was no evidence of growth or cellular proliferation of the tumor cells, nor evidence of cytokine production, nor evidence of systemic immunosuppression. The Executive Carcinogenicity Assessment Committee concluded that conventional 2-year bioassays were not needed for vedolizumab.

A reproduction study was performed in pregnant rabbits at single intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage) administered on gestation day 7 and revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. The non-clinical reviewers and the Maternal Health Team of the Pediatric and Maternal Health Staff (PMHS) have recommended a pregnancy category B for this product, and a pregnancy exposure registry as a PMC.

1. Conduct a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to Entyvio (vedolizumab) during pregnancy to an unexposed control population or collect Entyvio (vedolizumab) pregnancy exposure data by collaborating with an existing disease-based pregnancy registry.

A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage); however, adequate exposure and target saturation were not achieved in infants beyond 28 days. The non-clinical review team concluded that the existing non-clinical studies are not adequate to support pediatric clinical studies for the pediatric age group of 5 to 17 years. Therefore, they have recommended the following post-marketing required (PMR) study prior to the conduct of any studies in pediatric patients:

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

Vedolizumab was found in the milk of cynomolgus monkeys who were given doses at 25 times the human clinical dose, and no adverse effects were noted in infant monkeys (up to six months of age) born to mothers who received vedolizumab. PMHS has recommended the following PMC to better inform labeling:

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

Clinical Pharmacology Considerations

The pharmacokinetic (PK) and pharmacodynamic characteristics of vedolizumab in healthy subjects and subjects with UC or CD were demonstrated using the commercial product and the clinical trial product. Comparability was established between the two products, and similar PK characteristics were observed in UC and CD patients administered 300 mg vedolizumab as a 30 minute IV infusion on Weeks 0 and 2, followed by 300 mg vedolizumab every eight weeks starting from Week 6. The serum half-life of vedolizumab is approximately 25 days; there is minimal accumulation of the drug with chronic dosing. The population PK analysis results showed no clinically meaningful impact on PK for the following covariates: severity of disease state, body weight, serum albumin level, prior treatment with TNF- α antagonist therapy, age and co-administered medications.

The potential for concomitant immunomodulator therapies to impact vedolizumab's PK was evaluated using population PK data from phase 3 trials. The immunomodulator drugs tested

individually in the model were: azathioprine, methotrexate, mercaptopurine, and aminosalicylates. Concomitant immunomodulators appear to have no impact on vedolizumab PK based on the observed vedolizumab trough concentrations.

There was no statistically significant effect of concomitant medications on vedolizumab clearance; however, the applicant did not assess the potential for vedolizumab to impact the PK of other coadministered drugs. The OCP reviewer theorized that the potential exists for vedolizumab-induced improvements in inflammation and levels of circulating cytokines to indirectly impact the formation of CYP450 enzymes. For this reason, OCP has recommended that the applicant evaluate the disease-drug-drug interaction potential for vedolizumab and its effect on CYP substrate drug exposure in the UC and CD population, as a PMC:

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

A thorough QT/QTc study was performed for vedolizumab and was reviewed by the Interdisciplinary Review Team for QT Studies. The study dose (10 mg/kg) covered a margin of up to a 2.5-fold increase in exposure over the proposed clinical dose (~4 mg/kg). The upper bound of the 95% 1-sided confidence interval for the largest time-matched mean effect of vedolizumab on the QTc interval excluded 10 msec. No subject had QTc > 450 msec or had \geq 60 msec change in QTc from baseline. There was no evidence of an exposure-response relationship for QT prolongation. No events of clinical importance per ICH E14 guidelines occurred in the study.

The applicant conducted a study to evaluate the impact of vedolizumab on the immune system response. Study C13012 demonstrated that vedolizumab did not affect CD4+ and CD8+ lymphocyte counts or the CD4+:CD8+ ratio in the cerebrospinal fluid (CSF) of healthy subjects (N = 14) at 5 weeks after a single 450-mg infusion of vedolizumab. Vedolizumab concentrations in cerebrospinal fluid were measured in samples obtained prior to and 5 weeks after a 30-minute IV infusion of vedolizumab 450 mg. None of these samples had detectable vedolizumab in the CSF.

Efficacy

Ulcerative colitis

The efficacy of Entyvio was assessed in two randomized, double-blind, placebo-controlled trials (UC Trials I and II) in adult patients with moderately to severely active ulcerative colitis defined as a Mayo score of 6-12 with endoscopy subscore of 2 or 3. U.S.-enrolled patients had an inadequate response or intolerance to immunomodulator therapy and/or an inadequate

response, loss of response, or intolerance to a TNF- α blocker over the previous five-year period. Outside the U.S., prior treatment with corticosteroids was sufficient for inclusion if over the previous five-year period the patients were unable to successfully taper corticosteroids without a return of UC symptoms, or had an inadequate response or intolerance to corticosteroids. Patients who had received natalizumab ever in the past, and patients who had received a TNF- α blocker in the past 60 days were excluded from enrollment. Concomitant use of natalizumab or a TNF- α blocker was not allowed.

The age of enrolled patients ranged from 18 to 78 years, with a mean age of about 40 years. The majority of subjects were male (~59%) and Caucasian (>80%). Approximately one-third of patients were from the U.S.

In UC Trial I, 374 patients were randomized 3:2 to receive Entyvio 300 mg (n=225) or placebo (n=149) by intravenous infusion at Weeks 0 and 2. Efficacy assessment was conducted at Week 6. Concomitant administration of stable dosages of aminosalicylates, corticosteroids, and immunomodulators was permitted through Week 6.

In UC Trial I, a greater percentage of patients treated with Entyvio compared to patients treated with placebo achieved clinical response, clinical remission, and improvement of endoscopic appearance of the mucosa at Week 6.

Table 1. Proportion of Patients meeting Efficacy Endpoints at Week 6 (UC Trial I)

Endpoint	Placebo N=149	ENTYVIO N=225	p-value	Treatment Difference and 95% CI
Clinical response [†] at Week 6	26%	47%	<0.0001	22% (12%, 32%)
Clinical remission [‡] at Week 6	5%	17%	0.001	12% (5%, 18%)
Improvement of endoscopic appearance of the mucosa [§] at Week 6	25%	41%	0.001	16% (6%, 26%)

[†]Clinical response: reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ 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

[§]Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

Subgroup analyses for clinical response at Week 6 were conducted for: age, gender, race, duration of UC diagnosis, geographic region, baseline Mayo score, baseline fecal calprotectin, and disease location. There were no apparent differences in the magnitude of treatment benefit in these subgroups.

In UC Trial II, 373 patients who were in clinical response at Week 6 in UC Trial I were randomized 1:1:1 to one of the following regimens beginning at Week 6:

- Entyvio 300 mg by intravenous infusion every eight weeks (Q8W)
- Entyvio 300 mg by intravenous infusion every four weeks (Q4W)
- Placebo Q4W

Efficacy assessments were at Week 52. Concomitant aminosalicylates and corticosteroids were permitted through Week 52; concomitant immunomodulators were permitted outside the U.S., but were not permitted beyond Week 6 in the U.S.

In UC Trial II, a greater percentage of patients in groups treated with Entyvio compared to placebo achieved clinical remission at Week 52, and maintained clinical response (clinical response at both Weeks 6 and 52). Additionally, a greater percentage of patients in groups treated with Entyvio compared to placebo were in clinical remission at both Weeks 6 and 52, and had improvement of endoscopic appearance of the mucosa at Week 52. In the subgroup of patients who achieved clinical response at Week 6 and were receiving corticosteroids at baseline, a greater percentage of patients in groups treated with Entyvio as compared to placebo discontinued corticosteroids and were in clinical remission at Week 52.

Table 2. Proportion of Patients meeting Efficacy Endpoints at Week 52* (UC Trial II)

Endpoint	Placebo [†] N=126	ENTYVIO Every 8 Weeks N=122	p- value	Treatment Difference and 95% CI
Clinical remission at Week 52	16%	42%	<0.0001	26% (15%, 37%)
Maintenance of clinical response [§]	24%	57%	<0.0001	33% (21%, 45%)
Improvement of endoscopic appearance of the mucosa [#] at Week 52	20%	52%	<0.0001	32% (20%, 44%)
Clinical remission at both Weeks 6 and 52	9%	21%	0.0079	12% (3%, 21%)
Corticosteroid-free clinical remission [‡]	14% [‡]	31% [‡]	0.012	18% (4%, 31%)

*Patients must have achieved clinical response at Week 6 to continue into UC Trial II. This group includes patients that were not in clinical remission at Week 6.

[†]The placebo group includes those patients who received ENTYVIO at Week 0 and Week 2 and were randomized to receive placebo from Week 6 through Week 52

[§]Maintenance of clinical response: Clinical response at both Weeks 6 and 52

[#]Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability) at Week 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 (n=72 for placebo and n=70 for ENTYVIO every eight weeks). Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.

There was no difference in efficacy between the Q8W and Q4W dosing regimens relative to placebo.

Crohn's Disease

The efficacy of Entyvio was assessed in three randomized, double-blind, placebo-controlled trials (CD Trials I, II, and III) in adult patients with moderately to severely active CD defined as a Crohn's Disease Activity Index (CDAI) score of 220 to 450 points. CD Trials I and II contained a 6-week Induction Phase; however, only CD Trial I engaged two sequentially enrolled cohorts of patients. CD Trial II, although an induction study, had patients administered vedolizumab at Week 6 and explored a longer induction duration at Week 10. U.S.-enrolled patients had an inadequate response or intolerance to immunomodulator therapy and/or an inadequate response, loss of response, or intolerance to a TNF blocker over the previous five-year period. Outside the U.S., prior treatment with corticosteroids was sufficient for inclusion if over the previous five-year period the patients were unable to successfully taper corticosteroids without a return of UC symptoms, or had an inadequate response or intolerance to corticosteroids. Patients who had received natalizumab ever in the past, and patients who had received a TNF blocker in the past 60 days were excluded from enrollment. Concomitant use of natalizumab or a TNF blocker was not allowed.

In CD Trial I, 368 patients were randomized 3:2 to receive Entyvio 300 mg (n=220) or placebo (n=148) by intravenous infusion at Weeks 0 and 2. Efficacy assessment was conducted at Week 6. Concomitant administration of stable dosages of aminosalicylates, corticosteroids, and immunomodulators was permitted through Week 6. The median age of enrolled patients was 34.0 years. The majority of subjects were female (~53%) and Caucasian (89%). Approximately 24% of subjects were from the U.S.

In CD Trial I, a statistically significantly greater proportion of Entyvio-treated patients achieved clinical remission at Week 6 compared with patients who received placebo. The treatment difference between Entyvio and placebo was 7.8% (95% CI 1.2, 14.3; p = 0.0206).

Although a trend in favor of Entyvio was observed for the other primary endpoint of enhanced clinical response (defined as a ≥ 100 point decrease in CDAI from baseline) at Week 6, the difference between the Entyvio and placebo groups was not statistically significant. The treatment difference between Entyvio and placebo was 5.7% (95% CI -3.6, 15.0; p = 0.2322).

Table 3. Primary Efficacy Endpoints of Clinical Remission and Enhanced Clinical Response at Week 6

	Clinical Remission ^a		Enhanced Clinical Response ^b	
	PLA N = 148	VDZ N = 220	PLA N = 148	VDZ N = 220
Number (%) achieving endpoint	10 (6.8)	32 (14.5)	38 (25.7)	69 (31.4)
95% CI	(2.7, 10.8)	(9.9, 19.2)	(18.6, 32.7)	(25.2, 37.5)
Difference from placebo ^c		7.8		5.7
95% CI for difference from placebo		(1.2, 14.3)		(-3.6, 15.0)
P-value for difference from placebo ^d		0.0206		0.2322
Relative risk ^e		2.1		1.2
95% CI for relative risk		(1.1, 4.2)		(0.9, 1.7)

Subgroup analyses were conducted based on: age, gender, race, duration of UC, baseline CDAI, baseline C-reactive protein, geographic region, baseline fecal calprotectin, prior therapy, and disease location. For clinical remission at Week 6, the risk difference between treatment groups favored Entyvio only in the subgroup of patients who had baseline CDAI \leq 330 points.

In CD Trial II, 416 subjects were randomized 1:1 to receive Entyvio 300 mg (n=209) or placebo (n=207) by intravenous infusion at Weeks 0, 2 and 6. Of the total subjects enrolled, 75% had previously failed TNF- α antagonist therapy and approximately 25% were naïve to TNF- α antagonist therapy. The mean age was 37.9 years. The majority were female (57%) and Caucasian (90%). Approximately 28% were enrolled at sites in the US. Efficacy assessment was conducted at Week 6 in patients who had previously failed TNF- α antagonist therapy.

Concomitant administration of stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through Week 6.

In CD Trial II, the proportion of patients in clinical remission at Week 6 in the TNF- α antagonist failure ITT subpopulation was not statistically significantly different between the Entyvio and placebo groups. Of the 158 TNF- α antagonist failure patients who received Entyvio, 24 (15.2%) achieved clinical remission at Week 6 compared with 19 of 157 (12.1%) patients who received placebo. The treatment difference from placebo was 3.0% (95% CI: -4.5, 10.5; $p = 0.4332$).

Table 4. Clinical Remission at Week 6 TNF α Antagonist Failure ITT Subpopulation

Clinical Remission ^a	PLA N = 157	VDZ N = 158
Number (%) achieving clinical remission	19 (12.1)	24 (15.2)
95% CI	(7.0, 17.2)	(9.6, 20.8)
Difference from placebo		3.0
95% CI for difference from placebo ^b		(-4.5, 10.5)
P-value for difference from placebo ^c		0.4332
Relative risk ^d		1.2
95% CI for relative risk		(0.7, 2.2)

Since the primary efficacy endpoint did not reach statistical significance, formal hypothesis testing could not be performed for the ranked secondary endpoints. However, observed p-values, relative risks, and 95% confidence intervals are provided for descriptive purposes.

- In the overall ITT population, which included patients who had previously failed or were naïve to TNF- α antagonist therapy, 19.1% of Entyvio-treated patients and 12.1% of placebo-treated patients achieved clinical remission at Week 6; the treatment difference from placebo was 6.9% (95% CI: 0.1, 13.8; $p = 0.0478$).
- In the TNF- α antagonist failure ITT subpopulation, 26.6% of Entyvio-treated patients and 12.1% of placebo-treated patients achieved clinical remission at Week 10; the treatment difference from placebo was 14.4% (95% CI: 5.7, 23.1; $p = 0.0012$).
- In the overall ITT population, 28.7% of Entyvio-treated patients and 13.0% of placebo-treated patients achieved clinical remission at Week 10; the treatment difference from placebo was 15.5% (95% CI: 7.8, 23.3; $p < 0.0001$).

In CD Trial III, subjects who had achieved clinical response at Week 6 in CD Trial I, were randomized 1:1:1 to one of the following regimens beginning at Week 6:

- Entyvio 300 mg by intravenous infusion Q8W

- Entyvio 300 mg by intravenous infusion Q4W
- Placebo Q4W

Efficacy assessments were at Week 52. Concomitant aminosalicylates and corticosteroids were permitted through Week 52; concomitant immunomodulators were permitted outside the U.S., but were not permitted beyond Week 6 in the U.S.

Statistically significantly greater proportions of Entyvio-treated patients achieved clinical remission at Week 52 compared with patients who received placebo.

Table 5. Clinical Remission at Week 52 Maintenance Study ITT Population

Clinical Remission^a	PLA N = 153	VDZ Q8W N = 154	VDZ Q4W N = 154
Number (%) achieving endpoint	33 (21.6)	60 (39.0)	56 (36.4)
95% CI	(15.1, 28.1)	(31.3, 46.7)	(28.8, 44.0)
Difference from placebo ^b		17.4	14.7
95% CI for difference from placebo		(7.3, 27.5)	(4.6, 24.7)
P-value for difference from placebo ^c		0.0007	0.0042
Relative risk ^d		1.8	1.7
95% CI for relative risk		(1.3, 2.6)	(1.2, 2.4)

In addition:

- Statistically significantly greater proportions of Entyvio-treated patients achieved enhanced clinical response at Week 52 compared with patients who received placebo (p=0.0132).
- Statistically significantly greater proportions of patients treated with Entyvio achieved corticosteroid-free clinical remission at Week 52 compared with patients who received placebo (p=0.0154)

Durable clinical remission in CD Trial III was defined as clinical remission in $\geq 80\%$ of study visits, including the Week 52 visit (11 out of 13 study visits). No statistically significant differences were observed between Entyvio and placebo for the endpoint of durable clinical remission (p=0.1036), although a trend of treatment difference was observed in favor of Entyvio.

Among Entyvio-treated patients, in the sub-group of patients who had inadequate response, loss of response, or intolerance to a TNF- α antagonist versus patients who were TNF- α antagonist naïve, clinical remission rates at Week 52 were lower (28% versus 52%,

respectively), as were clinical response rates at Week 52 (29% versus 61%, respectively), and corticosteroid-free clinical remission rates at Week 52 (24% versus 40%, respectively).

There was no difference in efficacy between the Q8W and Q4W dosing regimens relative to placebo.

The clinical reviewer noted that exploratory analyses in the overall study population (i.e., patients who had previously failed or were naïve to TNF- α antagonist therapy), suggest that there may be a treatment effect in the overall study population. In addition, exploratory analyses in both the overall and TNF- α antagonist failure populations suggest that there may be a treatment effect at the later time point (Week 10).

The statistical team leader concluded that CD Trial I showed statistically significant benefit of Entyvio compared to placebo for the treatment of CD, as demonstrated by one of the induction primary efficacy endpoints, the maintenance (CD Trial III) primary efficacy endpoint and two of the three maintenance (CD Trial III) 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.

Safety

A total of 3,326 patients and healthy volunteers received at least one dose of Entyvio in the clinical trials, including 1279 patients with UC, 1850 patients with CD, and 197 healthy subjects. The safety review focused on the Phase 3 placebo-controlled trials and included 1,434 patients who received Entyvio 300 mg at Weeks 0 and 2 and then, starting at Week 6, Q8W or Q4W for up to 52 weeks and 297 patients who received placebo for up to 52 weeks. Of these, 769 patients had UC and 962 patients had CD.

The proportion of patients with at least one adverse event was 84% and 78% in the vedolizumab/vedolizumab (VDZ/VDZ), and placebo/placebo (PLB/PLB) groups, respectively. The most common adverse reactions, occurring in $\geq 3\%$ of ENTYVIO-treated patients and $\geq 1\%$ higher than in placebo-treated patients, were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, and cough.

One death (0.3%) occurred during the controlled clinical trial period in a patient receiving placebo, compared with 5 deaths in patients receiving Entyvio (0.3%). An additional 7 patients died in open-label extensions – 3 UC patients and 4 CD patients. None of these events appeared to be related to study drug. One death, a case of hepatocellular carcinoma in a 51 year-old female patient on Entyvio for 3 years, was assessed by the applicant as potentially related to the study drug.

Serious adverse events were reported in 19% of patients receiving VDZ/VDZ, compared to 13% receiving PLB/PLB. Serious infection adverse events that were considered drug-related

occurred with similar frequency between the Entyvio and placebo groups (3% and 2%). The most frequently reported SAEs were related to underlying IBD.

Adverse events leading to discontinuation were similar between the Entyvio and placebo groups.

Across the Phase 3 UC and CD trials, infusion-related reactions were reported by 4% of Entyvio-treated patients and 3% of placebo-treated patients. There was one case (0.07%) of anaphylaxis in an Entyvio-treated patient. While the incidence of hypersensitivity reactions in the clinical trials was low, the *Warnings & Precautions* section of product labeling will recommend that if anaphylaxis or other serious allergic reactions occur, administration of Entyvio should be discontinued immediately and appropriate treatment administered.

A higher proportion of Entyvio-treated patients than placebo-treated patients reported one or more infectious adverse events, 45% and 35%, respectively. In both the UC and CD populations, infections involving the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory infection) were the most commonly reported infections and occurred with greater frequency in Entyvio-treated versus placebo-treated patients. It is significant that oronasal-associated lymphocytes show $\alpha_4\beta_7$ expression, suggesting that MAdCAM-1 interactions have a role in nasal infections.

There was no increase in serious infections in the pooled UC and CD trials; however, among CD patients, serious infections were reported in 6% of VDZ/VDZ-treated patients and 3% of PLB/PLB-treated patients. Anal abscesses were the most frequently reported serious AEs among CD patients, occurring in 2% of Entyvio-treated patients versus <1% of placebo-treated patients.

The number of infections from enteric pathogens was small. There were no cases of *Listeria* or *Salmonella* in the placebo-controlled trials; however, there were 6 cases of *Clostridium difficile* infections and 2 cases of *Campylobacter* infections in Entyvio-treated patients versus none in placebo-treated patients. Herpes infections occurred in 3% of VDZ/VDZ-treated patients and 2% of PLB/PLB-treated patients; none was serious.

Product labeling will warn that patients treated with Entyvio are at increased risk for developing infections, and that Entyvio is not recommended in patients with active, severe infections until the infections are controlled. (b) (4)

t (b) (4) screening for TB (b) (4) should be considered.

PML has been observed with another integrin antagonist (natalizumab) and was intensively monitored for in the Entyvio clinical development program. Risk factors for the development of PML with natalizumab include longer duration of exposure, especially beyond 2 years, the presence of John Cunningham virus antibodies, and prior immunosuppressant use. Exposure to Entyvio through December 26, 2013 included 1056 patients exposed for ≥ 24 months, 627

patients for ≥ 36 months, and 155 patients for ≥ 48 months; 423 patients received concomitant immunosuppressants for ≥ 12 months, and 248 patients for ≥ 24 months. No cases of PML were identified in 3129 patients with a mean exposure to Entyvio of 18.1 months, which would exclude a risk of PML of up to 2.8/1000 patients exposed for ≥ 24 months. Product labeling will acknowledge that while no cases of PML were observed in the clinical trials, a risk of PML cannot be ruled out. Clinicians will be advised to monitor patients on Entyvio for any new onset, or worsening, of neurological signs and symptoms.

Natalizumab is associated with liver injury, including serious drug-induced liver injury (DILI). The mechanism of action for DILI with natalizumab is not fully understood. There were four cases of acute hepatocellular injury with Entyvio use during the clinical development program, of which one case in particular seemed related to drug treatment. Product labeling will warn of possible elevations of transaminases and/or bilirubin in patients receiving Entyvio, and to discontinue Entyvio in patients with jaundice or other evidence of significant liver injury. This risk will be further assessed in the post-marketing setting through enhanced pharmacovigilance.

To further characterize the safety of long-term exposure to Entyvio, FDA is requiring the applicant to conduct a post-approval prospective observational study, looking at serious infections (gastrointestinal and respiratory), PML and malignancies as outcomes of interest.

In addition, the applicant has agreed to a PMC to complete and submit the results of an ongoing open-label safety study:

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

And finally, the applicant will perform the following enhanced pharmacovigilance in addition to the reporting requirements in 21 CFR 600.80:

1. For a period of two years, the applicant will 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 will 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) will also be provided in the PBRER.

Immunogenicity

The immunogenicity of vedolizumab could not be reliably assessed during clinical development due to drug interference in the immunogenicity assay. The drug tolerance level of the immunogenicity assay was significantly less than the mean vedolizumab steady state trough concentrations during clinical trials, so the reported incidence of ADA is likely underestimated. While this deficiency does not preclude approval, FDA has asked and the applicant has agreed to conduct the following PMC:

1. A study to reanalyze banked immunogenicity serum samples from ulcerative colitis trial C13006 and Crohn's disease trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference.

ADA appeared to have an effect on the PK of vedolizumab. Six subjects with persistent ADA and available vedolizumab concentration data, all had substantial decreases in their serum concentrations of vedolizumab at Weeks 6 and 52. There were 8 patients with persistently positive ADA, and none of these patients achieved clinical remission at Weeks 6 or 52 in controlled trials.

The ability of ADA positive serum to neutralize the binding of vedolizumab to $\alpha_4\beta_7$ was examined using flow cytometry. Fifty-nine percent of the ADA-positive patients who received continuous vedolizumab in the maintenance phase developed neutralizing antibodies.

Pediatric Considerations

Pediatric Use. The safety and effectiveness of Entyvio have not been established in pediatric patients.

Required Pediatric Assessments. The pediatric study plan for Entyvio was discussed at a January 8, 2014 meeting of the Pediatric Review Committee (PeRC). The committee agreed with the recommendation from PMHS and the division to grant partial waivers to study pediatric patients less than 6 years of age with moderate to severe Crohn's disease and patients less than 5 years of age with moderate to severe ulcerative colitis. PeRC also agreed with the recommendation from PMHS and the division to grant a deferral of pediatric studies for all remaining age groups in each respective indication. The applicant will be required to conduct the following studies under the Pediatric Research Equity Act:

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

2. Conduct a randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by Entyvio (vedolizumab) in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis who have failed conventional therapy.
3. Conduct a randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by Entyvio (vedolizumab) in pediatric patients 6 to 17 years of age with moderately to severely active Crohn's disease who have failed conventional therapy.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Office of Prescription Drug Products, has concluded that the applicant's proposed tradename "Entyvio" is acceptable from both a promotional and safety perspective. In a letter dated August 20, 2013, Takeda Pharmaceuticals U.S.A., Inc. was notified that the proposed tradename was acceptable but that it would be re-reviewed 90 days prior to the approval of the BLA. DMEPA no longer re-reviews proposed proprietary names within 90 days of approval unless there is a change in the proposed product characteristics. Since none of the proposed product characteristics were altered, the proposed proprietary name is acceptable.

Advisory Committee

A joint meeting of GIDAC and the DSaRM AC took place on December 9, 2013. Discussion focused on efficacy results in the CD program; the adequacy of the safety database to exclude an unacceptable risk of PML; the indicated population; the role of concomitant immunosuppressant therapy; and the need for a REMS. The following questions were voted on by the committee:

1. Do the available data support the efficacy of vedolizumab for the proposed CD induction indication? YES – 12; NO – 9; ABSTAIN – 0

(The committee noted that the 10 week data were convincing.)

2. Do the available data support the efficacy of vedolizumab for the proposed CD maintenance indication? YES – 19; NO – 1; ABSTAIN – 1
3. Considering the currently available nonclinical and clinical data, has the applicant adequately characterized the potential risk of PML with vedolizumab to support approval? YES – 21; NO – 0; ABSTAIN – 0
4. If vedolizumab is approved, should concomitant immunosuppressants be limited to a specific duration (e.g., during induction only)? YES – 1; NO – 19; ABSTAIN - 1

5. 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 TNF α -antagonists? (13)
 - b. Patients that have failed immunosuppressants or TNF α -antagonists (i.e., the indicated population would not include patients that failed steroids only)? (8)
 - c. Neither a nor b. (0)
6. 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 TNF α -antagonists? (14)
 - b. Patients that have failed immunosuppressants or TNF α -antagonists (i.e., the indicated population would not include patients that failed steroids only)? (6)
 - c. Neither a nor b. (1)

The committee also discussed post-market risk mitigation strategies. Committee members urged that any post-market risk mitigation strategies required by FDA not be unduly burdensome for practitioners. The committee also recommended that FDA and the applicant attempt to quantify the risk of PML, in the post-market setting, as well as monitor for other serious infections.

REMS

The applicant proposed a Risk Evaluation and Mitigation Strategy (REMS) for Entyvio to mitigate the risk of PML. The proposed REMS consisted of a Communication Plan and a Medication Guide to inform healthcare professionals and patients about the potential risk of PML. Risk mitigation options were discussed at an October 2013 REMS Oversight Committee (ROC) meeting, the December 2013 joint GIDAC-DSaRM Advisory Committee meeting, and a February 2014 ROC meeting. Based on these discussions, FDA determined that the benefits of Entyvio outweigh the risks without a REMS. Several factors were considered in making this determination:

- the specificity of vedolizumab for binding to the $\alpha_4\beta_7$ integrin
- the selectivity of vedolizumab for inhibition of the $\alpha_4\beta_7$ -MAdCAM-1 interaction
- the lack of inhibition of CNS immune surveillance observed in the EAE model in Rhesus monkeys.

- the absence of an effect on CD4+ and CD8+ lymphocyte counts or the CD4+:CD8+ ratio in the cerebrospinal fluid (CSF) of healthy subjects, and the absence of detectable levels of vedolizumab in the CSF of healthy subjects administered vedolizumab.
- the absence of cases of PML in a large clinical trial database where PML was intensively monitored for.

The risk management strategy recommended by OND and OSE, in consideration of input from the GIDAC-DSaRM Advisory Committee members and the ROC, includes physician and patient labeling, enhanced pharmacovigilance, continuation of an ongoing long-term safety study, and a long-term post-marketing observational study.

Postmarketing Requirements under 505(o)

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

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

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

Therefore, based on appropriate scientific data, the applicant will be required to conduct the following:

1. A post-marketing, 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.

Conclusions

UC and CD are serious medical conditions with significant impact on patient morbidity, mortality and quality of life. Because many patients are unable to achieve sustained remission, or are intolerant to, or experience side effects from currently available treatment regimens, additional treatment options are needed.

In the UC population, Entyvio treatment was associated with statistically significant and clinically meaningful improvements in the induction and maintenance of clinical response; the induction and maintenance of clinical remission; the endoscopic appearance of the mucosa; and the achievement of corticosteroid-free remission.

In the CD population, efficacy data are less persuasive from a statistical point of view. The possible reasons for the modest effect observed in this population may be related to the disease itself, the extent of disease in the population studied, the enrollment of a large proportion of TNF- α antagonist failures, an inadequate dosing regimen, or the possible need for concomitant immunosuppressant therapy. The more modest benefit observed in this patient population will be reflected in the more limited indication of achieving clinical response; achieving clinical remission; and achieving corticosteroid-free remission. The applicant is strongly encouraged to conduct further study to better characterize the appropriate population and dosing regimen to induce and maintain clinical response and remission in patients with moderately to severely active CD.

The safety of Entyvio has been adequately characterized and has excluded an unacceptable risk of PML to support approval. Physician and patient labeling is sufficient to convey the known and theoretical safety concerns associated with Entyvio. The risk of PML and other potential safety issues associated with chronic use of Entyvio will be rigorously monitored in the post-marketing setting. Clinicians should be cautioned that no comparative claim of the safety of vedolizumab over natalizumab can be assumed, and there remains a risk of PML that can only be addressed after a large number of exposures over a long period of time have been observed.

DGIEP has recommended approval of BLA 125476 for Entyvio (vedolizumab) for 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 and for 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. All twenty-one

members of the joint GIDAC-DSaRM Advisory Committee recommended approval of Entyvio for the ulcerative colitis population, and 20 of 21 members recommended approval of Entyvio for the Crohn's disease population.

I concur with DGIEP's recommendation for approval, the PMRs/PMCs detailed in this memo, and the agreed upon labeling. Entyvio will fill an unmet medical need, and ongoing and required postmarketing studies will help clarify lingering uncertainty regarding its long-term safety.

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/s/

AMY G EGAN
05/20/2014