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RESEARCH**

APPLICATION NUMBER:

125476Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125476
Product Name: Vedolizumab

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>February 2015</u>
	Study/Trial Completion:	<u>August 2015</u>
	Final Report Submission:	<u>February 2016</u>
	Other: _____	<u>None</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The adult studies are completed and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To support the safety of vedolizumab in pediatric patients aged 5 to (b) (4) years.

The age of the monkeys used in 13-week and 26-week toxicology studies do not support the pediatric age group of 5- (b) (4) years. In the Pre and Post Natal Development (PPND) study in monkeys, adequate exposure and target saturation were not achieved in infants on postpartum (pp) days beyond 28 days. Vedolizumab was excreted at low levels into the breast milk of monkeys in this study. In addition, vedolizumab was detected only in one infant at 100 mg/kg on Day 120 pp, suggesting inadequate drug exposure to the infants during the entire observation period.

Overall, the existing nonclinical studies are not adequate to support pediatric clinical studies for the pediatric age group of 5- (b) (4) years.

Vedolizumab is a novel therapeutic agent with limited clinical experience, and a juvenile animal toxicology study in an appropriate species is required to support the proposed pediatric clinical studies in the pediatric age group of 5- (b) (4) years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 3-month repeated dose intravenous toxicology study in juvenile animals.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Ulcerative colitis and Crohn's disease are chronic, debilitating conditions which occur in children. There is a need for approved treatments for these diseases in pediatric patients. The goal of this phase 2 study is to assess the safety and tolerability of IV doses of vedolizumab in pediatric patients with UC and CD, as well as characterize the PK of vedolizumab in this patient population. The sponsor also intends to explore the relationship between disease activity and the dose/concentration of vedolizumab and use the data obtained to select the doses for the pediatric phase 3 trials planned in pediatric UC and CD.

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A dose ranging study to determine the PK, safety, and tolerability of vedolizumab in pediatric patients 5 through 17 years with moderate to severe UC and CD who have failed conventional therapy. There will be 3 cohorts stratified by weight across patients. The number of patients in each treatment group and age group must be reviewed and agreed upon with the Agency.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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If so, does the clinical trial meet the following criteria?

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- The trial will emphasize risk minimization for participants as the protocol is developed

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This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Ulcerative colitis and Crohn's disease are chronic, debilitating conditions which occur in children. There is a need for approved treatments for these diseases in pediatric patients. The goal of this Phase 3 study is to assess the safety and effectiveness of vedolizumab in pediatric patients with moderately to severely active Crohn's disease who have failed conventional therapy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by vedolizumab in pediatric patients 6 through 17 years with moderate to severe CD. The induction phase will be open-label; all responders will be randomized 1:1:1 at Week 14 to receive either placebo, lower- or higher-dose blinded maintenance therapy. The sample size is not intended to power hypothesis testing. Efficacy will be based on partial extrapolation from adult efficacy. The number of patients in each treatment group and age group must be reviewed and agreed upon with the Agency.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
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 - Other (provide explanation)
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Agreed upon:

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This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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Ulcerative colitis and Crohn's disease are chronic, debilitating conditions which occur in children. There is a need for approved treatments for these diseases in pediatric patients. The goal of this phase 3 study is to assess the safety and effectiveness of vedolizumab in pediatric patients with moderately to severely active ulcerative colitis who have failed conventional therapy.

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A randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by vedolizumab in pediatric patients 5 through 17 years with moderate to severe UC. The induction phase will be open-label; all responders will be randomized 1:1:1 at Week 14 to receive either placebo, lower- or higher-dose blinded maintenance therapy. The sample size is not intended to power hypothesis testing. Efficacy will be based on partial extrapolation from adult efficacy. The number of patients in each treatment group and age group must be reviewed and agreed upon with the Agency.

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(signature line for BLAs)

DEPI-I believes the theoretical risk of PML for vedolizumab, given that it is in the same class as natalizumab (which has a known serious risk of PML), is adequate to indicate an unexpected serious risk related to the use of vedolizumab. Although there was no clear increase in risk in malignancies based on the clinical data, longer term data is necessary to assess the unexpected serious risk of malignancies.

In addition, DEPI-I believes the observed imbalances in serious infections (such as respiratory and gastrointestinal infections) are adequate to indicate a signal of a serious risk related to the use of vedolizumab.

DEPI-I has 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). DEPI-I therefore requests a required post-marketing safety study (PMR) under section 901 of FDAAA 2007 Title IX to assess a signal of a serious risk of serious infections (such as respiratory and gastrointestinal infections) related to the use of vedolizumab and to identify the unexpected serious risks of PML and malignancies.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

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Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A post-marketing, prospective, observational, cohort safety study of vedolizumab versus other agents for inflammatory bowel disease.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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Continuation of Question 4

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- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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If so, does the clinical trial meet the following criteria?

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PMR/PMC Development Coordinator:

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(signature line for BLAs)

The goal of Trial C13008 is to determine the safety profile of long-term vedolizumab treatment. Important clinical events related to safety, such as serious infections and malignancy, are being collected. In addition, although no cases have been observed in vedolizumab clinical trials, another integrin antagonist (natalizumab) has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the CNS. Trial C13008 has already completed enrollment. The completion of the open-label trial will help to maximize the number of patients with at least 24 months exposure in order to better quantify the risk of PML.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

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Clinical Trial C13008 is ongoing and has completed enrollment (n = 2243). It is an open-label trial to determine the long-term safety of vedolizumab in patients with ulcerative colitis and Crohn's disease.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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- Other
Competition of open label trial
-

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PMR/PMC Development Template

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NDA/BLA # BLA 125476/Vedolizumab (ENTYVIO)
Product Name: _____

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>May 2015</u>
	Study/Trial Completion:	<u>May 2021</u>
	Final Report Submission:	<u>May 2022</u>
	Other: <u>Annual interim reports</u>	<u>05/20xx</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The adult clinical trials are completed and ready for approval.

Pregnant women were not included in the clinical trials. A pregnancy registry is recommended as this product is intended to be used chronically and by women of childbearing age. It is likely that the product will be used during pregnancy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this observational pregnancy exposure registry is to compare the pregnancy and fetal outcomes of women exposed to vedolizumab during pregnancy to an unexposed control population.

New drugs like vedolizumab generally have little or no human pregnancy experience prior to approval, unless the drug is specifically indicated for a pregnancy-related condition and obtaining human pregnancy data to adequately inform product labeling is important for all drug and biological products. Thus, collection of drug safety data on use during human pregnancy is often performed post-approval. The Food and Drugs Administration Amendments Act (FDAAA) of 2007 (see PL 110-85, Title IX, sec 905(a)(3)(C)(iv)) recommended complementary approaches to gather and analyze postmarketing data and information to assess the safety of use of a drug in domestic populations (such as in pregnant women) that were not included or underrepresented in the clinical trials used to approve a drug. Collecting meaningful pregnancy exposure data includes the establishment of a drug-based prospective cohort study (pregnancy exposure registry).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to vedolizumab during pregnancy to an unexposed control population. An acceptable alternative approach for collecting vedolizumab pregnancy exposure data is to collaborate with an existing disease-based pregnancy registry.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other

Pregnancy Registry

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 - There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # BLA 125476/Vedolizumab (ENTYVIO)
Product Name: _____

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>March 2015</u>
	Study/Trial Completion:	<u>March 2018</u>
	Final Report Submission:	<u>March 2019</u>
	Other: <u>n/a</u>	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The adult clinical trials are completed and ready for approval.

A clinical lactation study is recommended, as this drug is expected to be used by women of reproductive age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this milk only lactation study is to determine whether vedolizumab is present in breast milk when administered to lactating women.

Clinical lactation data should be available for drugs that are likely to be used in females of reproductive potential unless the drug has a known or potential serious safety concern that would preclude collection of such data. Nursing mothers labeling should adequately inform the use of a drug during lactation. Clinical lactation studies can be designed to assess the extent of drug into breast milk and the daily infant dose through breast milk; the severity and frequency of adverse events in breast-fed infants exposed to maternal drug through breast milk, and potential effects on milk production.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A milk-only lactation study in lactating women receiving vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk using a validated assay.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Milk lactation study
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 125476
Product Name: Vedolizumab

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 04/2015
Study/Trial Completion: 03/2016
Final Report Submission: 03/2017
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We recommend the applicant re-test banked immunogenicity serum samples from both UC and CD trials using an improved anti-drug antibody (ADA) assay. Vedolizumab interferes with ADA detection in the ELISA assay which prevents the detection of ADA as indicated by the higher immunogenicity incidence rate at 52 weeks (17%) post-treatment compared to during treatment (17% vs. 4%).

The recommended reanalysis is a PMC because the applicant did conduct immunogenicity assessment with methodologies available at the time of the clinical development program. However, more sensitive methodology has emerged over time which can be implemented readily and can overcome the drug interference issue with the ADA assay.

We also recommend that Takeda submits a technical report on the assay development and qualification for FDA review for suitability.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This recommendation is based on the finding of inadequate assessment of immunogenicity incidence in the current BLA. During our review, we identified that the immunogenicity rate was higher upon treatment discontinuation when compared to during treatment. Moreover, among subjects who were identified to be ADA positive, vedolizumab trough concentrations were reduced or becoming not detectable in those who have more than one time point with ADA+ findings during treatment. While these limited data indicated a negative impact of ADA on the PK, a full assessment of the impact of ADA cannot be conducted because of the inadequate ADA assay which may under report the ADA incidence due to drug interference. Preferably, ADA impact on PK and efficacy should be assessed once the reanalysis of immunogenicity samples is complete because the impact of ADA could not be reliably assessed in the current BLA submission but data in a small number of subjects suggest ADA may have negative impact on PK and efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

No new patients will need to be enrolled in a clinical trial to fulfill the PMC. The PMC study is to reanalyze already existing banked samples from UC trials using an improved ADA assay.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
assay development to further understanding of efficacy.

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 125476
Product Name: Vedolizumab

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 03/2015
Study/Trial Completion: 09/2019
Final Report Submission: 09/2020
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We recommend this as a PMC study as vedolizumab's efficacy and safety have been demonstrated in a patient population with unmet medical need. The study results may impact the safe and effective use of other concomitant CYP substrates, not the safe and effective use of vedolizumab itself.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This recommendation is based on the current understanding that CYP enzymes expression is suppressed by pro-inflammatory cytokines associated with inflammatory conditions, and they can normalize upon improvement of the inflammatory conditions. As a result, CYP substrates could have elevated exposure under inflammatory conditions and reduced exposure when disease condition is improved and the proinflammatory cytokines are normalized. The implication is a loss of efficacy of concomitant small molecule CYP substrate drugs which ulcerative colitis (UC) and Crohn's disease (CD) patients take. We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of UC or CD, an inflammatory disease condition, on the exposure of CYP substrate drugs (i.e., the disease drug interaction). Such a study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the Disease-DDI.

The USPI of tocilizumab contains information from a similar assessment in RA patients based on a single dose study. Results indicate a substantial alteration of CYP3A4 substrate; a single dose of tocilizumab reduced simvastatin exposure by about 60% at 1 week after dosing. Although data obtained after a single tocilizumab dose may under-estimate the extent of interaction, the results demonstrated the impact of pro-inflammatory cytokine normalization on the exposure of a small molecule CYP3A4 substrate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

We recommend a step-wise approach. The applicant can conduct a study to first define the impact of severe UC or CD disease condition on the exposure of CYP substrate drugs (i.e., the disease drug interaction). Such a study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent clinical study to evaluate the disease drug-drug interaction (Disease-DDI). Regarding the CYP substrate drugs (victim drugs), we recommend that the applicant evaluate multiple victim drugs as inflammatory disease conditions are known to have affected multiple CYP enzymes. We refer the applicant to the most recent guidance document entitled “*Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” for further information.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
Disease drug-drug interaction study.

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476/Entyvio (vedolizumab)

Product Name:

PMC #1 Description: To perform additional testing to confirm the monoclonality of the master cell bank.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2014</u>
	Other:	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Substance (DS) and Drug Product (DP) release specifications approved under the BLA are sufficient to ensure adequate quality and safety of vedolizumab for the initial marketed product. Assurance of the monoclonality of the vedolizumab producing master cell bank (MCB) will reduce the risk of the generation of product variants and ensure the consistency of vedolizumab product quality throughout the product life cycle.

2. Describe the particular review issue and the goal of the study.

The estimated probability of clonality does not provide sufficient assurance that the master cell bank (MCB) is derived from a single progenitor cell. During the product lifecycle minor changes made to the manufacturing process could result in outgrowth of subpopulations of cells that could impact product quality. The study will provide additional assurance of the consistency of the product quality through the additional testing to support the monoclonality of the MCB.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Additional characterization of the vedolizumab master cell bank (MCB) to support the monoclonality of the MCB.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

The Drug Product release specification approved under BLA is sufficient to ensure adequate quality and safety of vedolizumab for the initial marketed product. The addition of osmolality and Polysorbate 80 testing will support consistency of Drug Product formulation throughout continued manufacture.

2. Describe the particular review issue and the goal of the study.

The current drug product release specification includes some methods for evaluating drug product formulation, and validation studies for drug product formulation have been performed; however, the methods currently used for formulation assessment will only provide evaluation of a portion of the formulation components. The addition of osmolality and Polysorbate 80 testing will provide monitoring of the consistent addition of the remaining formulation components.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Qualification of the analytical methods for measuring the osmolality and polysorbate concentration of the Drug Product and the statistical analysis of the release data acquired using the qualified analytical methods.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476/ Entyvio (vedolizumab)

Product Name:

PMC #4 Description: 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.

PMC Schedule Milestones:

Final Protocol Submission:	MM/DD/YYYY
Study/Trial Completion:	MM/DD/YYYY
Final Report Submission:	02/29/2016
Other:	

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Product release specification approved under the BLA is sufficient to ensure adequate quality and safety of vedolizumab for the initial marketed product. The addition of a quantitative SDS-based method for assessing size-related impurities will provide better control of these impurities in DS and DP throughout the product lifecycle.

2. Describe the particular review issue and the goal of the study.

The current vedolizumab Drug Substance and Drug Product release specifications include a qualitative non-reduced SDS-PAGE assay that does not provide control over the amounts of size-related impurities. The addition of a quantitative non-reduced SDS-based method will provide consistent monitoring of the levels of low molecular weight size-related impurities in DS and DP throughout product lifecycle.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Validation of the quantitative non-reduced SDS-based method and statistical analysis of release data acquired using the new method.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476/Entyvio (vedolizumab)
Product Name:

PMC #5 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2014
	Other: _____	MM/DD/YYYY

NDA/BLA # 125476/Entyvio (vedolizumab)
Product Name:

PMC #6 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2014
	Other: _____	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 2013 OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern

- Manufacturing process analysis
- Other

The safety profile observed in clinical studies indicates that the presence of anti-drug antibodies does not appear to be a significant safety issue. The development and implementation of more sensitive assays for detecting binding and neutralizing anti-drug-antibodies (ADAs) would provide better assessment and characterization of the patients' ADA response to vedolizumab.

2. Describe the particular review issue and the goal of the study.

The current methods for detecting binding and neutralizing anti-drug antibody (ADA) are not tolerant to the presence of drug at the levels expected to be in some patients' serum at the time of sampling, leading to a reduced capability of detecting ADA. The development of more sensitive and drug tolerant assays for the detection of binding and neutralizing antibodies to vedolizumab would provide a more accurate measure and characterization of the patients' immune response to vedolizumab.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Development and validation of sensitive and drug tolerant methods to detect binding antibodies and neutralizing antibodies to vedolizumab in patients' serum samples.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

The current vedolizumab Drug Substance (DS) release specifications include an ELISA method for evaluating HCP levels in DS. This method detects various proteins from Chinese Hamster Ovary (CHO) cells, the general cell type used for manufacturing of vedolizumab. However, this method is not optimal for the detection of proteins from the vedolizumab producing CHO cell line. The implementation of an improved, product-specific HCP assay will provide more accurate control of the host cell related impurities in DS.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Development, validation and implementation of a product specific host cell protein assay including demonstration of improved sensitivity and capability to detect a greater range of potential host cell proteins compared to the current assay for vedolizumab.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476/Entyvio (vedolizumab)
Product Name:

PMC #8 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2016
	Other: _____	MM/DD/YYYY

PMC #9 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2018
	Other: _____	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Vedolizumab drug substance and drug product release and stability specifications approved under BLA are sufficient to ensure adequate quality and safety of vedolizumab for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Vedolizumab drug substance and drug product release and stability specifications are based on clinical and manufacturing experience provided in the BLA. However, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of vedolizumab release data acquired following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(Signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476
Product Name: ENTYVIO

PMC #1 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 21 CFR 314.101 OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Preliminary results do not show low endotoxin recovery for the previous drug substance (b) (4), (b) (4). The applicant plans to confirm those results using formulated drug substance in representative containers after the maximum hold time. Since the provisional results suggest no impact of formulated drug substance on endotoxin recovery, the risk for false endotoxin negatives in the finished product is deemed low.

2. Describe the particular review issue and the goal of the study.

The study will confirm preliminary data suggesting no impact of formulated drug substance in endotoxin recovery.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

To assess endotoxin recovery in formulated drug substance held under production conditions

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476
Product Name: ENTYVIO

PMC #1 Description: 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 time (b) (4)

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description:

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Preliminary results do not show low endotoxin recovery for the (b) (4). The applicant plans to confirm those results. Since the provisional results suggest no impact of the (b) (4) on endotoxin recovery, the risk for false endotoxin negatives in the finished product is deemed low.

2. Describe the particular review issue and the goal of the study.

The sponsor will confirm endotoxin recovery results for the (b) (4) and will establish endotoxin specification for the (b) (4). If low endotoxin recovery is found, the sponsor will establish maximum hold times for the (b) (4).

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

To assess endotoxin recovery studies on the (b) (4) added to the pre-formulated drug substance.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476
Product Name: Entyvio (Vedolizumab)

**Micro Drug Product
PMC #1 Description:** 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).

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/31/2014
Other: N/A

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

As detailed below in item 2, the Sponsor is being requested to perform studies to determine the minimum detectable leak size (perforation diameter) using the dye and microbial ingress test for the Vedolizumab container closure system. This value was not established during the validation studies submitted with the original BLA. In Amendment 125476/0.43, the Sponsor stated that completion of the requested studies within the review period was not possible, and that it was willing to conduct them as a PMC. A commitment was submitted 01/22/2014 in Amendment 125476/0.61.

2. Describe the particular review issue and the goal of the study.

During performance of the dye and microbial ingress validation studies for container-closure integrity, the Sponsor did not determine the minimum detectable leak size. Without knowledge of method sensitivity, the validity of the container integrity studies cannot be properly assessed. The goal of the requested studies will be to determine the minimum leak size detectable by the dye and microbial ingress methods and to optimize the methods for the detection of breaches (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

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), then alternative methods will be developed or the current methods will be optimized as necessary for the detection of breaches (b) (4). The target submission of a sensitive method for container closure integrity validation and final report will be 12/31/2014.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

APPEARS THIS WAY ON ORIGINAL



PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476
Product Name: Entyvio (Vedolizumab)

**Micro Drug Product
PMC #2 Description:** 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 worse case hold conditions. In the event kinetic turbidometric qualification studies demonstrate that acceptable endotoxin recoveries from the spiking studies are not achieved, the USP <151> rabbit pyrogen method will be used to release the finished drug product.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2014</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Long-term data needed.
- Theoretical concern
- Manufacturing process analysis
- Other

As detailed below in item 2, studies conducted by the Sponsor indicate that the vedolizumab drug product formulation can mask endotoxin detection by the USP <85> LAL kinetic turbidometric method. In Amendment 125476/0.79, the Sponsor committed to developing a validated LAL method that overcomes the masking effect, and stated that in the interim drug product release testing would be conducted by the USP <151> rabbit pyrogen method. The proposed studies are acceptable as a PMC rather than a pre-approval requirement because the rabbit method is a compendial method that can be used in lieu of the LAL assay.

2. Describe the particular review issue and the goal of the study.

Data presented in Amendments 125476/0.58 and 125476/0.68 indicated that the vedolizumab drug product formulation can mask endotoxin detection by the LAL kinetic colorimetric method. Preliminary data presented in Amendments 125476/0.68 and 125476/0.79 suggested that masking does not occur with the kinetic turbidimetric method., The goal of the study will be to qualify the kinetic turbidimetric method for (b) (4) testing of the bulk drug product and for release testing of the finished drug product.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

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. Submission of a qualified endotoxin LAL method will be completed by December 31, 2014. 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.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125476
Product Name: Entyvio (Vedolizumab)

**Micro Drug Product
PMC #3 Description:** 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)

PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 09/30/2014
Other: N/A

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Theoretical concern
- Manufacturing process analysis
- Other

As detailed below in item 2, studies conducted by the Sponsor indicate that Vedolizumab Drug Product (b)(4) can mask endotoxin detection by the USP <85> LAL kinetic chromogenic method. In Amendment 125476/0.79, the Sponsor committed to developing a validated LAL method that overcomes the masking effect. The proposed study is acceptable as a PMC rather than a pre-approval requirement because: (b)(4)
(2) the manufacturing process appears to be well controlled as evidenced by the microbiology quality data of (b)(4) and drug product batches produced to date; and (3) the level of endotoxin in the final drug product is assessed at release by the rabbit pyrogen method.

2. Describe the particular review issue and the goal of the study.

Data presented in Amendments 125476/0.58 and 125476/0.68 indicated that the Vedolizumab drug product formulation (b)(4) can mask endotoxin detection by the LAL kinetic colorimetric method. Preliminary data presented in Amendments 125476/0.68 and 125476/0.79 suggested that masking does not occur with the kinetic turbidimetric method. The goal of the study is to qualify the kinetic turbidimetric method and to demonstrate consistent endotoxin recoveries of spiked endotoxin from undiluted Vedolizumab Drug Product (b)(4) over worst case hold conditions in the relevant containers.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

To conduct studies to qualify an endotoxin assay for Vedolizumab Drug Product (b) (4)
Validation will be conducted with (b) (4) held under
worst case conditions in the relevant containers. The qualified methods will be
implemented for routine testing of the drug product (b) (4) The final report on the
endotoxin method qualification studies on drug product (b) (4) and
implementation for routine testing will be submitted by September 30, 2014.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

KEVIN B BUGIN
05/20/2014

ANIL K RAJPAL
05/20/2014



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

**Pediatric and Maternal Health Staff Review
Addendum to December 20, 2013 Review**

Date: April 29, 2014

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: ENTYVIO (vedolizumab) injection

BLA: 125476/125507

Subject: Pregnancy Exposure Registry and Clinical Lactation Study recommendations

In a review dated December 20, 2013, the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) provided suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling for ENTYVIO (vedolizumab) injection in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements. In that review, PMHS-MHT recommended a post-marketing requirement (PMR) for the collection of pregnancy exposure data in order to assess the safety of use of vedolizumab in pregnant women as this population was not represented in pre-marketing clinical trials and the drug will likely be used in females of reproductive potential. In addition, we recommended a post marketing commitment (PMC) for a milk-only clinical lactation study

using a validated assay conducted in lactating women who are using vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk in order to appropriately inform the Nursing Mother's subsection of labeling.

After further consideration, PMHS-MHT recommends the collection of pregnancy exposure data be included as a post marketing commitment (PMC) rather than a post marketing requirement (PMR) because there is no known serious risk, no signal of a serious risk, or unexpected serious risk based on a potential serious risk identified. Animal reproduction studies with vedolizumab failed to demonstrate a risk to the fetus and there are no adequate or well-controlled studies in pregnancy women. Often, new products like vedolizumab generally have little or no human pregnancy experience prior to approval, unless the product is specifically indicated for a pregnancy-related condition. However, obtaining human pregnancy data to adequately inform pregnancy labeling is important for all drug and biological products and should be obtained when possible. Options for collecting meaningful pregnancy exposure data include the establishment of a drug-based prospective cohort study (pregnancy exposure registry), collaboration with an established disease-based pregnancy exposure study, or enhanced pharmacovigilance with either an established pregnancy surveillance program or reporting and follow-up on known pregnancy exposures.

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/s/

CARRIE M CERESA
04/29/2014

JEANINE A BEST
04/29/2014

LYNNE P YAO
04/30/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Study Protocol

Date	January 24, 2014
Reviewer(s)	David Shih, MD, MS, Team Leader Division of Epidemiology 1
Division Director	Simone Pinheiro, ScD, MSc, Associate Division Director Division of Epidemiology 1 Office of Surveillance and Epidemiology Office of Pharmacovigilance and Epidemiology Center for Drug Evaluation and Research
Subject	Review of "A post-marketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel Disease"
Drug Name(s):	vedolizumab
Application Type/Number:	IND 9125, BLA 125476
Applicant/sponsor:	Takeda
OSE RCM #:	2012-1364

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EXECUTIVE SUMMARY

This review critiques the sponsor's submitted revised post-marketing study protocol to evaluate the long-term safety of vedolizumab and provides recommendations so the sponsor can revise and improve the protocol.

FDA is currently reviewing the biologics license application for vedolizumab, a $\alpha 4\beta 7$ -selective antagonist with proposed indications for Crohn's disease (CD) and ulcerative colitis (UC). The sponsor submitted a revised protocol (1) and participated in FDA's December 9, 2013, Gastrointestinal Drugs Advisory Committee meeting (GIDAC). The present review critiques the revised protocol, in light of the GIDAC discussions.

The study is a seven-year, prospective, observational, multi-center, North American, clinical cohort study of UC and CD patients comparing vedolizumab initiators with other-biologics initiators in a "real world" setting. The primary objective is to assess the long-term safety of vedolizumab. The primary outcome is adverse events of special interest, including serious infections including progressive multifocal leukoencephalopathy or PML, moderate and severe infections requiring antibiotics, malignancies, and infusion reactions.

The sponsor will use "subgroup analyses" to control for baseline disease severity and duration, prior or concomitant immunosuppressives or TNF- α inhibitor use, previous treatment with other monoclonal antibodies, prior disease exacerbation hospitalizations, prior disease-related surgeries, prior inflammatory bowel disease (IBD) drug failures, IBD therapy duration, prior infection, prior vaccination status, and malignancy history.

The analyses will estimate descriptive statistics, outcome cumulative incidences, and risk ratios. An expected sample size of 2,500 in each exposure arm corresponds to 80 percent statistical power to detect a serious infection relative risk of 1.6.

The review finds:

- 1) *The sample size projection lacked adequate explanation of methods and assumptions.*
- 2) *The protocol lacks descriptions of key study components.*
- 3) *Although a logical treatment alternative, the TNF- α inhibitor class comparator precludes direct estimate of vedolizumab-attributable outcome risk.*
- 4) *The protocol lacks mechanisms for dealing with medication switching or discontinuation, leaving the results susceptible to exposure misclassification bias.*
- 5) *The power calculation uses inappropriate assumed incidence density rates.*
- 6) *The anticipated time is too short to fully study malignancy outcomes.*
- 7) *The proposed study lacks a testable hypothesis and outcome case definitions.*
- 8) *After receiving input during and after the advisory committee meeting, alternative study outcomes might include one or more of: bacterial pneumonia, influenza, liver injury, epidermal and skin conditions, paresthesias and dysesthesias, Clostridium difficile diarrhea or colitis, tuberculosis, Campylobacter gastroenteritis, cytomegalovirus colitis, Listeria meningitis, sepsis, and death.*

- 9) *Effectiveness-related outcomes might be difficult to interpret in an observational study.*
- 10) *The implicit proposed hypothesis test, detecting an elevated outcome risk, might result in a study more difficult to interpret than a study with a hypothesis test ruling out an elevated outcome risk.*
- 11) *A completely different analysis, combining all available longitudinal exposure data (both pre and post-marketing), might better assess PML risk.*

Although a good starting-point, the sponsor-submitted protocol lacks sufficient detail to determine whether such a study might yield interpretable results.

To the sponsor, we recommend providing missing key study design components; adding a non-vedolizumab, non-TNF α inhibitor comparator; revising sample size calculations; and clarifying the plan to study malignancy with short follow-up times. To DGIEP, we recommend assessing PML risk as a broader effort (using data from multiple sources), using caution in interpreting efficacy outcomes in observational studies, and continuing dialog among stakeholders to clarify the desired study outcomes. For further details, see Section 6 RECOMMENDATIONS of this document.

1 INTRODUCTION

This review critiques the sponsor's submitted revised post-marketing study protocol to evaluate the long-term safety of vedolizumab and provides recommendations so the sponsor can revise and improve the protocol.

1.1 BACKGROUND

Vedolizumab is a α 4 β 7-selective monoclonal antibody integrin antagonist submitted as a new molecular entity biologic license application. FDA is considering approving it for the proposed indications:

- Reducing signs and symptoms, inducing and maintaining clinical response, clinical remission, and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor alpha (TNF α) antagonist in Adult patients with moderately to severely active ulcerative colitis as defined by the Mayo Score
- Reducing signs and symptoms, inducing and maintaining clinical response, clinical remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor alpha (TNF α) antagonist in Adult patients with moderately to severely active Crohn's disease as defined by the CDAI

Proposed dosing is 300 mg infused intravenously over approximately 30 minutes at 0, 2, and 6 weeks, and then every 8 weeks thereafter.

1.1.1 Crohn's Disease

From the CD clinical review,

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

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

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

Other treatment options in this population of moderately to severely active CD include corticosteroids, immunomodulators, TNF α -antagonists (infliximab, adalimumab, and certolizumab) and natalizumab. The number of patients that have received natalizumab for CD is very small (approximately 1,100). The natalizumab indication is limited to patients that have failed TNF α -antagonists.” (2)

1.1.2 Ulcerative Colitis

From the UC BLA clinical review,

“Ulcerative colitis (UC) is a chronic relapsing inflammatory disease of the rectal and colonic mucosa, which is characterized by clinical remissions and exacerbations resulting from intestinal inflammation. The typical age of onset for UC is between the ages of 15 and 30, and over 450,000 people in the United States (US) may be affected. (Loftus EV. Inflammatory Bowel Disease, 2007; 13(3):254-261) While the pathogenesis of UC is not completely understood, abnormal leukocyte trafficking to the GI mucosa is believed to be an important component leading to colonic inflammation.

Symptoms can vary depending on the severity of inflammation and extent of disease; however, patients typically experience recurrent episodes of rectal bleeding and diarrhea, often associated with crampy abdominal pain and tenesmus. Symptoms are often followed by periods of remission, which may be spontaneous or as a result of treatment. Patients may also exhibit systemic symptoms including fever, malaise, and weight loss; and severe colitis can result in ischemic colitis requiring surgical colectomy. Colectomy is considered curative in UC, but it is associated with significant morbidity, including recurrent pouchitis in up to 25% of patients, fecal incontinence, and female infertility.

Finally, patients with long-standing UC are at increased risk for colorectal cancer. The goals of UC treatment are to induce and maintain remission of clinical symptoms and mucosal inflammation in order to improve quality of life, decrease hospitalizations, and reduce the risk of surgery and colon cancer. (Hoentjen F, et al., *Curr Gastroenterol Rep* 2011;13:475-485)

The treatment options for UC are dictated by the severity of clinical symptoms and the anatomic extent of disease. Patients with mild to moderate UC are typically treated with topical and oral aminosalicylates, as well as topical steroids. Oral corticosteroids may be required in patients who are refractory to these treatments or who are systemically ill and require more rapid treatment. Immunomodulators such as azathioprine and mercaptopurine can be considered for patients not responding to or dependent on oral corticosteroids and for those who relapse on aminosalicylates.

Available treatments for moderate to severe disease include corticosteroids, immunomodulators, and monoclonal antibodies targeting TNF- α . There are three currently approved anti-TNF agents for UC, infliximab, adalimumab, and golimumab. These agents provide an important treatment option for patients with moderate to severe UC who have failed other therapies; however none has been shown to achieve sustained remission in more than 30% of patients (Hanauer et al 2002, Sandborn et al 2005); and in clinical trials, patients who had failed 1 anti-TNF agent had a significantly lower response to subsequent anti-TNF therapy. (Thomson AB 2012;18(35) *World J Gastro*)”(3)

1.1.3 Tysabri (natalizumab)

From the UC BLA clinical review,

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

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

As per the current label for Tysabri, three factors that are known to increase the risk of PML in Tysabri-treated patients have been identified:

- (1) Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment.
- (2) Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- (3) Presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.

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

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

At the time of approval for CD, one of the post-marketing commitments (PMCs) was for a prospective observational study (CD INFORM) that specified that at least 2,000 CD patients must be enrolled, and that a least 1,000 patients must have two years of Tysabri treatment. CD INFORM was designed primarily to determine the incidence and pattern of serious and/or clinically significant infections, malignancies, and other serious adverse events (SAEs) in patients with Crohn's disease (CD) treated with natalizumab; the main safety outcome of interest in CD INFORM is PML. At the time of this review, the accrual of the study has been limited by the use of the marketed product in CD, and a total of only 187 subjects have been enrolled. Additional data is not yet available.”(3)

Vedolizumab is in the same biologics class as natalizumab. However, vedolizumab purportedly is more selective than natalizumab and there are no known cases of vedolizumab-associated PLM. Therefore, PML remains a theoretical risk of vedolizumab.

1.2 REGULATORY HISTORY

On June 7, 2000, the sponsor submitted the original IND for vedolizumab. In January 2006 PML concerns prompted the natalizumab withdrawal from the U.S. market and an FDA clinical hold on all integrin antagonists including vedolizumab. FDA lifted the clinical hold in July 19, 2007. Other key elements of the regulatory history are:

- | | |
|----------------------|--|
| June 21, 2012 | Sponsor submitted an initial proposed postmarket observational study protocol outline. |
| July 19, 2012 | I completed a review of the submitted protocol outline. |
| July 24 and 25, 2012 | Type C industry meeting occurred. Sponsor and FDA discussed the protocol in general terms. |
| June 20, 2013 | Sponsor submitted final clinical data for the vedolizumab BLA and a revised observational study protocol. |
| December 9, 2013 | Gastrointestinal Drugs Advisory Committee (GIDAC) meeting |
| December 19, 2013 | Industry meeting occurred in which Office of Drug Evaluation III Director, Dr. Julie Beitz, posed sample size questions to the sponsor |

January 17, 2013 Sponsor submitted written response to Dr. Beitz's questions (see APPENDIX A: Sponsor's January 17, 2014, Response to FDA's Sample Size Questions).

CDER offices tabled internal postmarketing requirement (PMR) epidemiology studies until after the GIDAC meeting because it likely was to heavily influence PMR study planning. This review critiques the revised protocol, accounting for points discussed at the GIDAC. The original PDUFA goal date was February 18, 2014. However, it will occur three months later than planned due to a late sponsor BLA submission.

2 REVIEW METHODS AND MATERIALS

The main review document was the sponsor's submitted revised protocol, "A post-marketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease." (1)

I also referred to the following documents:

Gottlieb, Klaus T. Clinical review: Klaus Gottlieb BLA 125476 Entyvio (vedolizumab). 3428850, 1-152. 12-30-2013. Silver Spring, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Office of Drug Evaluation III, Division of Gastrointestinal and Inborn Errors Products.

Muldowney, Laurie. Clinical review: Laurie Muldowney BLA 125476 Entyvio (vedolizumab). 3410494, 1-156. 11-20-2013. Silver Spring, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Office of Drug Evaluation III, Division of Gastrointestinal and Inborn Errors Products.

Lichtenstein, Gary R, Feagan, Brian G, Cohen, Russell D, Salzberg, Bruce A, Diamond, Robert H, Price, Samiyeh, Langholff, Wayne, Londhe, Anil, and Sandborn, William J. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol* 107, 1409-1422. 2012

I referred to FDA's guidances on pharmacoepidemiology (4) and PMR studies (5) in assessing whether the protocol adheres to best practices.

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The study is a seven-year, prospective, observational, multi-center, North American, clinical cohort study of UC and CD patients comparing vedolizumab initiators with other-biologics users in a "real world" setting. The primary objective is to assess the long-term safety of vedolizumab. The secondary objective is characterizing changes in UC or CD disease activity. The primary outcome is adverse events of special interest, including serious infections, moderate and severe infections requiring antibiotics, malignancies, and infusion reactions. Researchers will collect disease activity data using IBD and quality of life questionnaires.

The sponsor anticipates controlling, using subgroup analyses, for baseline disease severity and duration, prior or concomitant immunosuppressives or TNF- α inhibitor use, previous treatment with other monoclonal antibodies, prior disease exacerbation hospitalizations, prior disease-related surgeries, prior IBD drug failures, IBD therapy duration, prior infection, prior vaccination status, and malignancy history.

In addition to descriptive statistics, the analyses will estimate outcome cumulative incidences and risk ratios. The protocol fails to mention time-to-event or time-varying analysis. The sponsor plans to enroll 2,500 in each exposure arm, corresponding to 80 percent statistical power to detect a serious infection relative risk of 1.6. See also APPENDIX B: Study Summary Table for a tabular study synopsis.

3.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The stated primary objective is “To assess the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD.”

Stated secondary objectives are “To describe changes in UC/CD disease activity using disease activity scores, health resources used, and quality of life (QoL) results, during the course of the study.”

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

The study is a prospective, observational clinical cohort study. The protocol fails to describe clearly whether the design is a true inception cohort.

3.3.1.2 Population & Time Period

The study population will be comprised of adult (≥ 18 years) CD and UC patients in multiple unspecified North American centers. Data collection occurs in routine medical office visits at 1) baseline and 2) at least as often as every six months. See also APPENDIX D: Baseline Data Collected, APPENDIX E: Post-Baseline Data Collected, and APPENDIX F: Recommended Assessments Schedule for the relevant information.

The protocol states a seven-year study period. Subject follow-up lasts until study termination. The protocol lacks other censoring criteria and a recruitment period description.

3.3.1.3 Selection, Inclusion and Exclusion Criteria

3.3.1.3.1 Inclusion Criteria

For inclusion, patients must initiate either 1) vedolizumab for an approved indication or a 2) biologic agent for UC or CD.

The protocol failed to define initiation (the number of preceding months required to be study drug-free) and to state whether prior vedolizumab exposure disqualifies a comparator biologic initiator (or vice-versa).

The protocol also failed to describe a recruitment plan, but included an appendix of Possible Retention Strategies. Strategies generally focused on relationship-building with subjects.

Providing a welcome packet, obtaining secondary contact information, distributing newsletters, and creating a patient rewards program are all listed strategies. The list also includes tracking reasons for missed visits, “Establishing a patient investigator transfer and transition plan for patients who change health care providers,” and Direct-to-Patient Contact (methods to obtain data directly from the patient).

3.3.1.3.2 Exclusion Criteria

Researchers will exclude subjects with any of the following:

- Enrollment in a protocol-managed clinical trial of CD or UC treatment
- Prior vedolizumab treatment
- Patient unsuitability, determined by Investigator judgment

3.3.1.4 Protected Health Information (PHI) Requirements

Researchers plan to obtain informed consent upon enrollment and permission to abstract medical records. Investigators are responsible for obtaining independent review board (IRB) approval.

3.3.2 Outcome & Exposure

3.3.2.1 Exposure

The *exposure* is Vedolizumab. The *comparator drugs* are the TNF α antagonists, adalimumab or certolizumab pegol by subcutaneous injection, or infliximab by IV infusion. Data collection includes investigator-reported drug used, indication, dose received, route of administration, and use dates.

In this observational study, researchers do not assign treatment. Instead, patients and doctors determine treatment (exposure) in the course of routine medical care.

3.3.2.2 Outcomes

The primary outcomes are adverse events of special interest. The definition, from the protocol,

“Serious infections (infections that are SAEs, including PML)

- Other clinically significant infections, not SAEs, that are classified as moderate or severe (Section 8.1.2) and require antibiotic treatment
- Malignancies
- Infusion-related reactions”

Protocol section 8.1.2 classifies severity as:

- “Mild: An AE that is easily tolerated and does not interfere with daily activities.
- Moderate: An AE that is sufficiently discomforting so as to interfere with daily activities.
- Severe: An AE that prevents normal everyday activity. Note that “severe” is not synonymous with ‘serious’: an AE may be assessed as severe without meeting the criteria for an SAE”

The protocol lists “All other SAEs” and “Adverse reactions” as other outcomes.

To address the secondary objective, IBD activity assessment, data collection includes

- Partial Mayo score (for UC patients) or HBI score (for CD patients)
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)
- Quality of life (QoL) assessments, using the standard research questionnaires, SIBDQ and SF-12

The protocol failed to list censoring criteria, likely because it lacks time-to-event analysis (see Section 3.3.5 Statistical Analyses).

3.3.3 Covariates

3.3.3.1 Confounders

The sponsor chose potential confounders by identifying factors that might have associations with outcomes. The potential covariate-outcome relationships listed are:

- Prior or concomitant *immunosuppressives or TNF- α inhibitor use and PML, opportunistic infections, or malignancy*
- *Malignancy history and new incident malignancy*
- *Prior infection or vaccination status and opportunistic infections*
- *Previous treatment with other monoclonal antibodies and infusion-related reactions.*

“If deemed appropriate,” the protocol calls for “subgroup analyses,” to control for the covariates. It also proposed to use baseline data in the subgroup analyses and relative risk calculations “to explore these possible associations” but failed to describe these explorations.

3.3.3.2 Effect Modifiers

Researcher chose potential effect modifiers by identifying factors that might increase the safety events risk in the study period. The sponsor identified, as potential effect modifiers

- Baseline disease severity, as evidenced by disease activity scores
- Prior hospitalizations for disease exacerbation and prior disease-related surgeries
- Prior TNF- α antagonists treatment
- Prior IBD drug failures
- Select (but unspecified) IBD therapy duration
- Disease duration at enrollment.

As in Section 3.3.3.1 Confounders, the protocol mentioned subgroup analyses, “if deemed appropriate,” but failed to describe the analyses or criteria for appropriateness.

3.3.4 Sample Size/Power

3.3.4.1 Sample Size Calculation Assumptions

Expected discontinuation proportion: 55% during the first 2 years and 10% thereafter

Background serious infection rate: 1.42 per 100 person-years

Exposed group serious infection rate: 2.06 per 100 person-years

Exposure: 2812 patient-years

Alpha: 0.05

The Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry study provided exposed group and background rates - infliximab treatment group and other treatments group respectively.(6)

3.3.4.2 Estimated Sample Size

Researchers estimate *2,500 subjects per exposure category has 80% power to detect a serious infection RR of 1.6 for vedolizumab compared with other biologics.* For power curve see APPENDIX C: Sponsor's Submitted Graph, Statistical Power vs. Detectable Relative Risk. Furthermore, at least 1,000 patients will have at least 24 months follow-up.

3.3.5 Statistical Analyses

The sponsor plans to finalize a statistical analysis plan (SAP) "prior to data base lock."

The sponsor will present descriptive statistics – 1) for continuous variables, outcome count, mean, standard deviation, median, minimum, and maximum and 2) for categorical variables, frequency (count and percent).

The primary analysis estimates the risks of AESI (see Section 3.3.2.2 Outcomes, above) as

$$\text{Outcome} = \text{Total Outcome Count} / \text{Number at Risk}$$

The protocol fails to describe time-dependent analyses, although it states "The safety outcomes also will be assessed by duration of exposure to determine whether reported events are time dependent." Researchers plan to estimate 95% confidence intervals (CIs), also.

Primary analysis estimates vedolizumab vs. comparator relative risk (RR), adjusting for "important confounders such as disease severity." The protocol lacked a description of statistical adjustment methods beyond the subgroup analyses mentioned in Section 3.3.3 Covariates, above, and ever-exposed patients to natalizumab.

The protocol calls for analyzing key safety results after 50 percent of the expected vedolizumab population receives at least 1 year of treatment.

4 DISCUSSION

- 1) *The sample size projection lacked adequate explanation of methods and assumptions.* The protocol merely states the projected attrition rates and total recruitment. FDA

requires reasonable assurance the study's sample size will allow for both adequate statistical power and PML risk bounding (see the Discussion points on statistical power and PML, below). Also, understanding the subject recruitment over time helps FDA understand how quickly the sponsor will collect and analyze data on large numbers of subjects.

- 2) *The protocol lacks descriptions of key study components.* Beyond components mentioned in the points above, missing are plans for subject recruitment, dealing with missing data, procedures to follow patients who switch to non-investigator physicians, and patient death ascertainment. Further absent are a study drug initiation definition (particularly the look-back “clean period” and whether prior use of vedolizumab disqualifies an other-biologic initiator and vice-versa), recruitment period definition, and a clear specification of the primary statistical analysis method. Finally, the protocol failed to account for potential confounding by indicated disease (certolizumab has a CD but not a UC indication) and exposure duration (natalizumab users, with at least 24 months exposure, are at greater PML risk than users with shorter exposures).
- 3) *Although a logical treatment alternative, the TNF- α inhibitor class comparator precludes direct estimate of vedolizumab-attributable outcome risk.* On the December 19, 2014 teleconference, the sponsor justified their study (lacking biologic-free comparator) by stating researchers already characterized TNF- α attributable risk well. Presumably, the sponsor is referring to the CD Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry data. TREAT is an observation cohort study of 3,420 patients on infliximab compared to 2,853 patients, on other treatments, followed a mean of 5.2 years. The study occurring from 1999 through February 2010. Infliximab patients were at higher risk for serious infections compared to other treatments (adjusted HR=1.43, 95% CI 1.11, 1.84). However it might be difficult to compare present-study subjects with TREAT study subjects. TNF- α and vedolizumab-naïve patients today might have different outcome risks compared those during the TREAT study time period. Furthermore, without a mechanism to follow subjects off both vedolizumab and comparator, investigators following the protocol might unnecessarily discontinue the subject from the study. Adding an additional such comparator group can improve the study's interpretability.
- 4) *The protocol lacks mechanisms for dealing with medication switching or discontinuation, leaving the results susceptible to exposure misclassification bias.* The planned outcome occurrence statistic, cumulative incidence, fails to account for time on drug. The protocol assumes initiators stay on the drug from enrollment to study termination – an Intent to Treat (ITT) analysis. This assumption lacks compatibility with “real world” conditions, where patients might start, stop, switch, or combine study drugs. Instead the ITT framework leads to misclassification bias, especially if an infliximab-initiator experiences an outcome while on vedolizumab. This exposure misclassification bias, assuming it is non-differential, results in bias toward the null. Time-varying exposure variable can help address study drug switching and discontinuation – particularly with relatively acute events, such as infections and infusion reactions. Delayed outcomes such as occurrence of

malignancies generally require different analytical methods, possibly similar to the protocol's subgroup analysis of vedolizumab ever-users.

- 5) *The power calculation uses inappropriate assumed incidence density rates.* The assumed rates came from the TREAT registry (6), specifically serious infection incidence densities among infliximab patients and other treatments only subjects. However, the sponsor makes a different comparison – vedolizumab vs. other biologics (mostly TNF- α inhibitors like infliximab). Therefore, a more appropriate comparator rate is the TREAT infliximab serious adverse event incidence density. The appropriate exposure rate is an estimated incidence density, possibly using clinical trial data. More appropriate incidence density rate assumptions might lead to a greater (if the effect size is smaller) or lower (because of a higher background rate) required sample size. Furthermore, the protocol lacks adequate explanation of the sample size and statistical power calculations. Finally, the calculated power assumes recruitment goal achievement. The power estimate fails to be valid for smaller sample sizes.
- 6) *The anticipated time is too short to fully study malignancy outcomes.* The sample size calculation assumes total exposure time to be 2,812 person years with 2,500 vedolizumab users – a mean exposure time of 1.1 years. The protocol fails to distinguish between exposure and follow-up time, suggesting they are the same. Malignancies are believed to develop over long periods of time. However, the product development program has not discovered a vedolizumab signal for malignancy so far. Including it as a study outcome might be unnecessary.
- 7) *The proposed study lacks a testable hypothesis and outcome case definitions.* According to FDA's postmarketing studies guidance, "To facilitate interpretation of the findings, the studies should always have a protocol, should include a control group, and should test prespecified hypotheses." (5) Lack of a prespecified, testable hypothesis hinders interpretation after the study. Furthermore, FDA's pharmacoepidemiology guidance emphasizes the need to develop medically and scientifically relevant case definitions. (4) At the December 19, 2014, sponsor teleconference, I announced that FDA expects clear clinical case definitions in the final study protocol. The sponsor responded they would be happy to accommodate us by stating any MedRA codes we desired. I then explained that case definitions are more than a list of MedRA codes, but a clear description, identifying cases in person, place, and time, with clinical criteria. They might include biopsy results, radiography, or laboratory testing. Lack of case definitions can lead to outcome misclassification bias and, assuming it is non-differential, bias toward the null. Granted, the protocol's broad outcomes (e.g., severe infections, serious adverse events) are hard to define. However, as stakeholders come to consensus on specific outcomes of interest, the protocol can include better-defined case definitions, possibly while making serious infections as the primary outcome.
- 8) *After receiving input during and after the advisory committee meeting, alternative study outcomes might include one or more of: bacterial pneumonia, influenza, liver injury, epidermal and skin conditions, paresthesias and dysesthesias, Clostridium difficile diarrhea or colitis, tuberculosis, Campylobacter gastroenteritis, cytomegalovirus colitis, Listeria meningitis, sepsis, and death.* Stakeholders have yet

to identify a single, specific infection as the predominant infection of concern (PML is a different matter and requires different methods – see the final Discussion point, below). Furthermore, the TREAT study found an elevated risk of serious infections among its biologic (infliximab) users. Therefore, the broad category, serious infections, might be a reasonable primary outcome. The sponsor submitted the protocol before the December 9, 2014, GIDAC meeting. Therefore, the proposed primary outcomes lack the benefit of important stakeholder discussions.

- At the GIDAC meeting, the chairman, Dr. Steven Solga, feared PML concerns might overshadow other important safety issues, “I feel like sponsor’s been on the hook for PML way too hard and way too long, but to some degree, off the hook for other concerns.” He also expressed concern over specific respiratory tract infection safety issues, “I’m not so concerned about nasopharyngitis, but influenza, MRSA, pneumonia, pneumococcus are real diseases that people actually die from.” (7) Clinical trials showed an increase in nasopharyngitis incidence in vedolizumab patients compared to placebo (13 percent vs. 17 percent). Furthermore, influenza, sinusitis, oropharyngeal pain, and cough all had 2 percent risk differences between study arms. See APPENDIX G: Sponsor-Proposed Adverse Event Labeling. The sponsor postulated vedolizumab interference with Nasal Associated Lymphoid Tissue as a possible mechanism. (2)
- At the same meeting, GIDAC member Dr. Avindra Nath expressed similar sentiments, “PML is not what I’m really worried about, but there are a whole host of other infections in these patients. You had patients with bronchopneumonia, with sepsis or died, and there’s one case of listeria meningitis. These are the kinds of things we never saw with natalizumab, but you’re seeing them with these patients.” He further expressed concern over autoimmune hepatitis. (7) Dr. Laurie Muldowney’s UC clinical review, noted two cases of potential drug-related or autoimmune liver toxicity. Liver toxicity has occurred after natalizumab use. She called for labelling, close postmarket monitoring, and possibly enhanced pharmacovigilance.(3)
- In his Crohn’s Disease vedolizumab clinical review, Dr. Klaus Gottlieb listed two as safety issues meriting further investigation. “Paresthesias and dysesthesias (MEDDRA High Level Term) were observed in 2.79 % of 718 vedolizumab treated patients in study C13007 and there were no reports in 148 placebo treated patients. This corresponds to an odds ratio of 8.7 (95 % CI 0.5 – 144.9) with a nominal p-value of 0.035.” He noted 1) the elevated risk appeared only in the CD study (C13007) and not the UC study, and 2) exploratory analysis uncovered this odds ratio. The sponsor postulated drug-induced autoimmune processes or inflammatory bowel disease, itself, as possible mechanisms. Finally, Dr. Gottlieb recommended measuring CD34+ cells’ response to vedolizumab administration and, after CBER consultation, possibly collecting nasopharyngeal samples to detect IgA and IgM antibodies.
- Dr. Gottlieb also deemed “epidermal and skin conditions” worthy of further investigation. In the CD study, the MEDDRA High Level Group Term

(HLGT) “skin appendage conditions” occurred among 6.3 percent of vedolizumab subjects and 2.0 percent of placebo arm patients - odds ratio of 3.2 (95 % CI 1.0 -16.5) and nominal p-value of 0.046. In the UC study, HLGT “epidermal and dermal conditions” occurred among 14.7 % vedolizumab subjects (n= 576) versus 8.1 % of placebo subjects (n=149). The odds ratio was 2.0 (95 % CI 1.0 –4.0), corresponding to a nominal p-value of 0.041. He speculated vedolizumab might interfere with skin T-cell function somehow. (2)

- At the GIDAC, the sponsor presented specific infection incidence density data (see APPENDIX H: Serious Infection Incidence Density in Vedolizumab Clinical Trials). Highest in incidence density were *Clostridium difficile* diarrhea or colitis, tuberculosis, *Campylobacter* gastroenteritis, cytomegalovirus colitis. Tuberculosis was the least frequent of these events. We expect between 2 and 3 tuberculosis cases, assuming 2,812 person-years vedolizumab exposure.

9) *Effectiveness-related outcomes might be difficult to interpret in an observational study.* Observational studies are susceptible to confounding by indication, that is, factors making subjects more likely to select one medication also influence the risk of the outcome. This type of confounding can be especially challenging in efficacy studies, where the outcome might have a close association with the indication.

10) *The implicit proposed hypothesis test, detecting an elevated outcome risk, might result in a study more difficult to interpret than a study with a hypothesis test ruling out an elevated outcome risk.* We have asked the Division of Biometrics VII (DB7) for advice on power calculations. Biostatisticians, Drs. John Yap Clara Kim, recommend changing the “detecting” hypothesis test to a “ruling-out” one. The protocol’s sample size section describes a calculation showing the ability to *detect* an RR of 1.6 with 80% power, a description consistent with a superiority hypothesis test (H0: RR=1 vs. H1: RR>1). The two possible study results are

- Failing to reject the null hypothesis, RR=1 or absence of elevated risk (but the results fail to inform us that risk in the two cohorts are the same) or
- Rejecting the null hypothesis, no elevated risk, but data are only consistent with RR>1 (not a prespecified elevated risk level).

A non-inferiority hypothesis study (H0: RR>=x vs. H1: RR<x, where x is the risk to rule out) results in either

- Failing to reject the null hypothesis, RR of at least x (lack of evidence to rule out an RR of x or greater) or
- Rejecting the null hypothesis, RR of at least x (*ruling out* an RR of x or greater).

Although easier to interpret, a non-inferiority hypothesis study might require a larger sample size. Furthermore, consensus, on the appropriate RR to rule out, is difficult to achieve. Discussions with DB7 are ongoing as we consider how to formulate the hypothesis test.

11) *A completely different analysis, combining all available longitudinal exposure data (both pre and post-marketing), might better assess PML risk.* PML is exceedingly rare. In the absence of AIDS or severe immunosuppression, we expect no PML cases. For instance, most of our biologic-related PML knowledge comes from multiple sclerosis natalizumab data. At the GIDAC, FDA-invited speaker, Dr. Eugene Major, stated "...we have never seen PML in an MS population unless that individual has been treated with natalizumab, regardless of whether or not the patient had been treated with prior immunosuppressive therapy or was serologically positive." To characterize PML risk, a TOUCH-like registry would be the optimal study design, because it would provide complete exposure data and participation among vedolizumab users. In the absence of a TOUCH-like registry, the proposed study's has strengths and limitations in its ability to evaluate REMS-related safety issues. See the table immediately below.

<u>Strengths</u>	<u>Limitations</u>
of an observational study with comparator and no TOUCH-like registry	from lacking a TOUCH-like registry
ETASUs' absence might lead to increased vedolizumab uptake	Voluntary vedolizumab user study enrollment and follow-up rates likely will be lower compared to mandatory registry rates
Vedolizumab user sample size adds to the PML safety database of exposed users	The vedolizumab user study population might not represent the entire user population
Comparator group allows us to evaluate associations with more common AEs	Vedolizumab dosing history might be less complete

Table. Proposed Study's Strengths and Limitations Compared to a TOUCH-Like Registry

The proposed study's strengths stem from its comparator and lack of a TOUCH-like registry:

- *ETASUs' absence might lead to increased vedolizumab uptake.* If patients and physicians are free of regulatory access restrictions, more patients likely will use vedolizumab compared to a counterfactual situation where access restrictions are in place. More greater use might lead to a larger sample size than expected had there been access restrictions.
- *Vedolizumab user sample size adds to the PML safety database of exposed users.* Although not a complete registry of users, the proposed study follows a vedolizumab user cohort and aims to ascertain exposures and PML outcomes. These data can add to the data from other studies to help us better understand vedolizumab-associated PML risk.
- *Comparator group allows us to evaluate associations with more common AEs.* The proposed study's comparator group is an advantage over a single-exposure

registry. The comparator allows investigation of other adverse events with a nonzero expected background rate. Most adverse events of stakeholder concern fall into this category, including liver injury and non-PML serious infections. See Discussion point 8, above, for an adverse events listing.

The proposed study also has limitations from lacking a TOUCH-like registry:

- *Voluntary vedolizumab user study enrollment and follow-up rates likely will be lower compared to mandatory registry rates.* TOUCH requires all users to participate just to receive natalizumab. As a result, TOUCH can collect data on all users. The proposed study lacks a mechanism to require participation, so the study will enroll a fraction of all users. Furthermore, patients might switch to non-investigator physicians, limiting follow-up.
- *The vedolizumab user study population might not represent the entire user population.* TOUCH includes all users and, by definition, represents the user population. Due to voluntary study enrollment, self-selection might occur, potentially leading to an unrepresentative exposed population and limited generalizability.
- *Vedolizumab dosing history might be less complete.* TOUCH allows for ascertainment the date of every administered dose. In the proposed study the investigators must remember to document each dose, which might have occurred up to six months prior to the office visit. Exposure misclassification might occur.

Researchers can study extremely rare outcomes, like PML, in studies lacking a control group, *especially with well-conducted enhanced pharmacovigilance.* Because researchers failed to identify any PML cases among vedolizumab patients, the rule of threes yields an upper bound for the risk estimate (i.e. upper risk bound is $1/(3n)$, where n is the total subjects observed). Therefore, although this study can contribute useful data, we recommend using all available longitudinal data sources to inform PML risk understanding.

5 CONCLUSION

Although a good starting-point, the sponsor-submitted protocol lacks sufficient detail to determine whether such a study might yield interpretable results.

6 RECOMMENDATIONS

6.1 RECOMMENDATIONS TO THE SPONSOR

- 1) Please add to the protocol:
 - a. A clear explanation of the sample size projection. Include assumptions used. Justify uptake and attrition rates (including a table demonstrating historical clinical trial subject attrition). Include graphs showing, over time, projections of total vedolizumab subject recruitment and subjects with at least 24 months vedolizumab exposure.
 - b. Estimated duration from study start to interim analysis
 - c. Plans for:

- i. Subject recruitment
 - ii. Dealing with missing data
 - iii. Procedures to follow patients who switch to non-investigator physicians
 - iv. Patient death ascertainment.
- d. Study drug initiation definition (particularly the look-back “clean period” and whether prior use of vedolizumab disqualifies an other-biologic initiator and vice-versa)
 - e. Recruitment period definition
 - f. Clear specification of the primary statistical analysis method
 - g. Methods to control for indicated disease (UC vs. CD) and exposure duration
 - h. A non-TNF- α , non-vedolizumab comparator group
 - i. Methods for dealing with study drug switching or discontinuation (such as time-varying exposure variable analysis)
- 2) Please revise the power calculation section
- a. Because the proposed study’s *comparator* group comprises TNF- α inhibitors users, use the TREAT study’s infliximab incidence densities for an assumed *comparator rate*. For the vedolizumab rate, estimate the incidence density using the best available vedolizumab safety data.
 - b. Explain how you calculated statistical power. Include formulas, references, assumptions, and statistical software used. Provide enough detail to enable FDA to replicate your calculation.
 - c. Provide power curves to account for scenarios in which the actual recruited sample size differs from the predicted sample size.
- 3) Please clarify the assumed average follow-up in light of the malignancy outcome. The sample size calculation assumptions include 2,500 vedolizumab users and 2,812 person-years exposure. Because the protocol fails to distinguish between exposure and follow-up time, we estimate a mean follow-up of 1.1 years. How will you study a long-latency outcome like malignancy with such a short follow-up time?
- 4) In the final study protocol, FDA expects a testable hypothesis and clear, clinical case definitions. We understand the difficulty of developing hypotheses and case definitions before consensus on outcomes of stakeholder concern. As future discussions between FDA and Takeda develop, we will better understand which specific outcomes are the most important to study. This understanding will enable you to develop a meaningful testable hypothesis and medically and scientifically relevant case definitions.

6.2 RECOMMENDATIONS TO DGIEP

- We recommend directing the sponsor to study outcomes in as specific language as possible. The more specific the outcome, the clearer the case definition can be. Stakeholders have expressed concern over *bacterial pneumonia, influenza, liver injury, epidermal and skin conditions, paresthesias and dysesthesias, CD34+ count,*

nasopharyngeal IgA and IgM, Clostridium difficile diarrhea or colitis, tuberculosis, Campylobacter gastroenteritis, cytomegalovirus colitis, Listeria meningitis, sepsis, and death. A composite primary outcome of serious infections might be reasonable. However, I also would like to see the sponsor study additional, more specific outcomes. We look forward to further discussions among CDER divisions to help guide the PMR study.

- We urge caution in interpreting effectiveness outcomes in observational studies, such as the present, sponsor-proposed study.
- Consider whether a hypothesis *ruling out* a prespecified comparative risk level is more appropriate than a *detecting* one. On January 17, 2014, FDA sent the sponsor the comments from section 6.1, Recommendations to the Sponsor. We await the sponsor's power calculation clarifications and have yet to achieve consensus on a primary outcome. In the meantime, we will continue discussing, with DB7, how to best formulate the hypothesis test.
- To evaluate vedolizumab-associated PML risk, instead of solely relying on the proposed study, we recommend a separate analysis using all available data sources with well-characterized exposures. The rare nature of the PML outcome allows us to study PML risk in the absence of a control group, *especially with well-conducted enhanced pharmacovigilance*. Data from the present proposed study can add to the clinical trial data, open label extension studies, and any registries that might arise in the future.

CC: Dal Pan G, Iyasu S, Slatko G, Do P / OSE

Wang C, Pinheiro S, Shih D, Campbell R, Calloway P / DEPI I

Manzo C, Mehta R, Worthy K, Neyarapally G / DRISK

Proestel S, Wu Ling-Wu, Fine A, Cao C / DPV I

Beitz J, Egan A / ODE III

Griebel D, Korvick J, Rajpal A, Muldowney L, Bugin K / DGIEP

Levenson M, Kim C, Yap J / DB7

7 REFERENCES

1. Xue S. A post-marketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease. Deerfield (IL): Takeda Pharmaceutical Company Limited; 2013 May 16. 1-56 p.
2. Gottlieb KT. Clinical review: Klaus Gottlieb BLA 125476 Entyvio (vedolizumab). Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Office of Drug Evaluation III, Division of Gastrointestinal and Inborn Errors Products; 2013 Dec 30. Report No.: 3428850. 1-152 p.

3. Muldowney L. Clinical review: Laurie Muldowney BLA 125476 Entyvio (vedolizumab). Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Office of Drug Evaluation III, Division of Gastrointestinal and Inborn Errors Products; 2013 Nov 20. Report No.: 3410494. 1-156 p.
4. Guidance for industry and FDA staff: best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. Silver Spring (MD): U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER); 2013 May. i-31 p.
5. Guidance for industry: postmarketing studies and clinical trials — implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. Silver Spring (MD): U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research; 2011 Apr. 1-18 p.
6. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, Langholff W, Londhe A, Sandborn WJ. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol* 2012;107:1409-22.
7. Transcript: GIDAC and DSaRM Advisory Committees, December 9, 2013. Silver Spring (MD): U.S. Department of Health and Human Services, FDA Center for Drug Evaluation & Research ; 2014 Jan 3. 1-390 p.
8. Briefing document for the joint meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee: Vedolizumab for the treatment of ulcerative colitis and Crohn's disease. Deerfield (IL): Takeda Pharmaceuticals U.S.A.; 2013 Dec 4. 1-243 p.

APPENDIX A: SPONSOR'S JANUARY 17, 2014, RESPONSE TO FDA'S SAMPLE SIZE QUESTIONS

Agency Question 1:

In follow up to the December 19, 2013 teleconference between FDA and Takeda, Takeda received a request on 15 January 2014 by telephone to provide to the BLA a rationale for the assumptions that supported the sample size calculations for the proposed protocol MLN-0002_401, "A post-marketing, prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease."

Company Response 1:

The sample size for the planned study (Protocol MLN-002_401) was chosen to provide a reliable estimation of incidence rates for uncommon SAEs and AESI. The proposed sample size was determined through consideration of: 1) the expected rates of SAEs/AESI; 2) the feasibility of enrollment based on the projected market uptake of vedolizumab; and 3) the observed attrition rates during the vedolizumab clinical program. An overall sample size of 2500 patients was selected, which allows us to exclude events occurring at a rate greater than 1.2 per 1000 patients using the "Rule of 3". Takeda also wanted to exclude an increased risk of serious infections with vedolizumab compared to standard of care using the comparator arm of the study. It is established that epidemiological studies may not provide robust relative-risk estimates below relative risks of 1.5 due to the potential for confounding by indication, and that this may be particularly relevant for drugs with a new mechanism of action. Therefore the sample size was estimated based on a wish to have approximately 80% power to exclude a relative risk of 1.6, based on the serious infection rates seen in the TREAT study. The rate of serious infections with other biologic treatments for moderately to severely active IBD was taken from the TREAT study which provides 5 year serious infection rates for patients with CD treated in clinical practice rather than using the rate in patients who only satisfied clinical trial inclusion and exclusion criteria. More rigorous clinical study inclusion and exclusion criteria can tend to underestimate rates of rates of certain adverse events in clinical studies compared to those seen in clinical practice, and therefore Takeda considered that clinical practice rates would be more appropriate for determining sample size requirements for MLN-0002_401.

The assumptions behind the sample size calculation are therefore the rate of serious infections on other treatments used for moderate to severe IBD, a relative risk exclusion of 1.6, a type 1 error of 0.05 and power of 80%. Further details on the sample size calculations are provided in the MLN-0002_401 protocol, Section 6.5.

Finally, in order to further characterize long term safety of vedolizumab, the study will include sufficient numbers of patients to ensure that at least 1,000 vedolizumab treated patients will have at least 2 years of study exposure. This will mean that Takeda can continue monitoring the safety of vedolizumab in the post approval period. It will also allow us to exclude long term risks occurring at a rate of 3 per thousand considering this study alone, but when combined with the more than 1000 patients treated for 2 years or more in study C13008, means we can exclude risks occurring at a rate of greater than 1.5 per 1000, using the "Rule of 3".

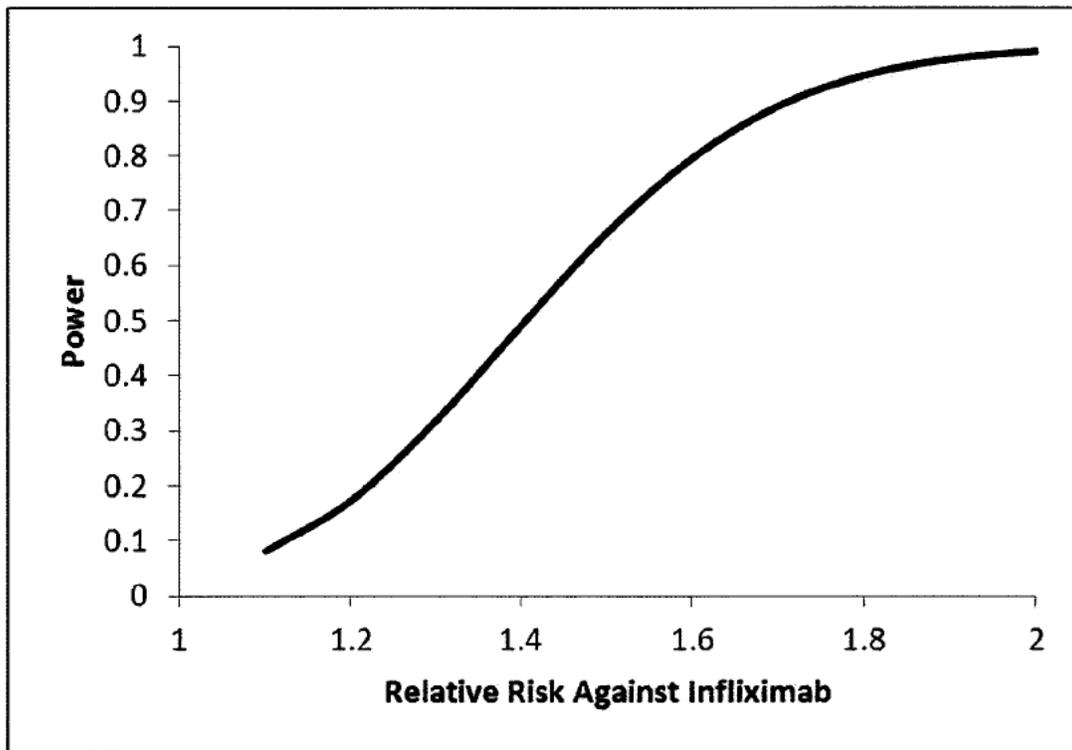
APPENDIX B: STUDY SUMMARY TABLE

Table 1 – Design Summary

	Study
1.1 Objectives/Aims/Scope	Primary: assessing vedolizumab long-term safety Secondary: characterizing disease activity changes
1.2.1 Design	
1.2.1.1 Type	Observational, clinical cohort study of UC and CD
1.2.1.2 Data Source	Prospectively-collected clinical office data
1.2.1.3 Time Period	7 years, unspecified recruitment period
1.2.1.4 Criterion (Selection) Standards	Inclusion: patients must initiate either <ul style="list-style-type: none"> • vedolizumab for an approved indication or • Other biologic agent for UC or CD. Exclusion: <ul style="list-style-type: none"> • CD or UC treatment clinical trial participation • Prior vedolizumab treatment • Investigator-determined patient unsuitability
1.2.2 Setting	Multi-center, North American, routine office visits
1.2.3 Exposure	vedolizumab initiators vs. other-biologics used to treat UC or CD
1.2.4 Outcome(s)	Safety outcomes <ul style="list-style-type: none"> • Adverse Events of Special interest: Serious infections, other moderate or severe infections requiring antibiotic treatment, malignancies, infusion-related reactions • All other SAEs • Adverse reactions IBD activity, measured by <ul style="list-style-type: none"> • Partial Mayo score (UC) or HBI score (CD) • Health resources used • SIBDQ and SF-12
1.2.5 Covariates	<ul style="list-style-type: none"> • Baseline disease severity and duration

	<ul style="list-style-type: none"> • Prior or concomitant immunosuppressives or TNF-α inhibitor use • Previous treatment with other monoclonal antibodies • Prior disease exacerbation hospitalizations • Prior disease-related surgeries • Prior IBD drug failures • IBD therapy duration • Prior infection • Prior vaccination status • Malignancy history
1.2.6 Sample Size	<p>N=2,500 in each exposure arm</p> <p>Beta = 0.20 to detect a serious infection relative risk of 1.6, assuming background rates and effect sizes from the CD TREAT registry, 55% drop-out in the first year, and 10% annually thereafter</p>
1.2.7 Statistical Analyses	<p>Descriptive statistics</p> <p>Outcome cumulative incidences and risk ratios. The protocol fails to mention time-to-event or time-varying analysis.</p> <p>The sponsor describes methods to control for covariates only as “subgroup analyses.”</p>

APPENDIX C: SPONSOR'S SUBMITTED GRAPH, STATISTICAL POWER VS. DETECTABLE RELATIVE RISK



Source: Sponsor's submitted study protocol (1)

APPENDIX D: BASELINE DATA COLLECTED

Demographic data

Medical history:

- General, including comorbid conditions and other autoimmune disease(s)
- Prior serious and atypical infections and dates
- Malignancies
- Organ transplantation, including bone marrow or stem cell transplants

UC/CD history, including:

- Dates and age of onset / diagnosis
- Disease location(s)
- Presence of extraintestinal manifestations
- Surgical history / disease management
- Health resources used within 1 year before study enrollment (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)

IBD activity assessment:

- Partial Mayo score for patients with UC
- HBI score for patients with CD

Any prior use of the following categories of drugs, including specific drug used, indication, dose received, route of administration, and dates of use:

- TNF- α antagonists, azathioprine, 6-mercaptopurine (6-MP), methotrexate, 5-aminosalicylic acid (5-ASA), or any approved IBD medication
- Any agents that have a known association with PML(alemtuzumab, belatacept, brentuximab vedotin, efalizumab, etanercept, infliximab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)

Prior use of other immunomodulatory, anti-neoplastic, or immunosuppressive agents for IBD, including specific drug used, dose received, route of administration, and dates of use, within 5 years before study enrollment

Prior use of other immunomodulatory, anti-neoplastic, or immunosuppressive agents for other indications, including specific drug used, indication, dose received, route of administration, and dates of use, within 5 years before study enrollment

Prior use of systemic corticosteroids, including specific drug used (if known), indication, dose range, route of administration, and dates of use, within 6 months before study enrollment

Prior use of antibiotics to treat UC/CD, including specific drug used, dose received, route of administration, and dates of use, within 5 years before study enrollment

QoL assessments:

- SIBDQ

- SF-12

History of infusion-related reactions

Source: sponsor's protocol (1)

APPENDIX E: POST-BASELINE DATA COLLECTED

The sites will record the following data at least every 6 months during the study, and at additional visits if needed for management of disease exacerbation, according to standard practice in other long-term observational studies of patients using biological drugs for treatment of UC and CD. If additional, unscheduled visits are performed, the minimum data to be recorded are SAEs, AESI, and adverse reactions.

Treatment and/or study discontinuation: date, reason (e.g., AEs, surgery, death, loss of efficacy)

Vedolizumab infusions, including dose and dates

Any use of the following categories of drugs, including specific drug used, indication, dose received, route of administration, and dates of use:

- TNF- α antagonists, azathioprine, 6-MP, methotrexate, 5-ASA, or any approved IBD medication
- Any agents that have a known association with PML (alemtuzumab, belatacept, brentuximab vedotin, etanercept, infliximab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)

Use of systemic corticosteroids, including specific drug used (if known), indication, dose range, route of administration, and dates of use

Use of antibiotics to treat UC/CD, including specific drug used, dose received, route of administration, and dates of use

IBD activity assessment:

- Partial Mayo score for patients with UC
- HBI score for patients with CD

Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)

QoL assessments:

- SIBDQ
- SF-12

AESI:

- Serious infections (infections that are SAEs, including PML)

- Other clinically significant infections, not SAEs, that are classified as moderate or severe (Section 8.1.2) and require antibiotic treatment
- Malignancies
- Infusion-related reactions

All other SAEs

Adverse reactions

Female patients are required to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy and neonatal condition:

- Pregnancy history (date confirmed)
- Pregnancy outcome (full-term, pre-term, fetal loss/stillbirth, miscarriage, induced abortion)
- Neonatal characteristics:

Apgar scores (if known)

Respiratory distress or other complications

Admission to Neonatal Intensive Care Unit / length of stay

Congenital anomalies

Source: Sponsor's protocol (1)

APPENDIX F: RECOMMENDED ASSESSMENTS SCHEDULE

	Baseline	At Least Every 6 Months:(a)
Informed consent	X	
Demography	X	
Medical history, including comorbid conditions and other autoimmune disease(s), prior serious and atypical infections, malignancies, and organ transplantation, including bone marrow or stem cell transplants	X	
UC/CD history, including dates and age of onset / diagnosis, disease location(s), extraintestinal manifestations, surgical history / disease management, and health resources used due to IBD within 1 year before study enrollment	X (b)	
Prior use of TNF- α antagonists, azathioprine, 6-MP, methotrexate, 5-ASA, systemic corticosteroids, antibiotics for UC/CD, or any approved IBD medication	X	
Prior use of agents that have a known association with PML	X	
History of infusion-related reactions	X	
Health resources used due to IBD (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)		X
Vedolizumab or other biologic treatment administration	X	X
Any use of TNF- α antagonists, azathioprine, 6-MP, methotrexate, 5-ASA, systemic corticosteroids, antibiotics for UC/CD, or any approved IBD medication		X
Any use of agents that have a known association with PML		X
IBD activity assessment: Partial Mayo score for patients with UC HBI score for patients with CD	X	X (c)
QoL assessment (SIBDQ, SF-12)	X	X (c)
SAEs		X (a)
AESI		X (a)
Adverse reactions		X (a)
Pregnancy and neonatal characteristics (females only):		X
Pregnancy history: Date confirmed, vedolizumab exposure at estimated time of conception, vedolizumab exposure during pregnancy		X (d)
Pregnancy outcome: Full-term, pre-term, fetal loss/stillbirth, miscarriage, induced abortion		X (e)
Neonatal characteristics: Apgar scores (if known), Respiratory distress or other complications, admission to neonatal intensive care unit / length of stay, congenital anomalies		X (d)

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AESI = adverse event(s) of special interest; CD = Crohn's disease; GI = gastrointestinal; HBI = Harvey-Bradshaw Index; QoL = quality of life; SAE = serious adverse event; SF-12 = 12-Item Short Form Health Survey; SIBDQ = Short Inflammatory Bowel Disease Questionnaire; TNF- α = tumor necrosis factor alpha; UC = ulcerative colitis

(a) If additional, unscheduled visits are performed, the following data should be recorded, at a minimum: SAEs, AESI, and adverse reactions.

(b) Within 1 year before study enrollment

(c) To be collected at the routine GI visit nearest to the 6-month time point

(d) To be reported as information becomes available

(e) To be reported within 30 days after delivery

Source: Sponsor's protocol (1)

APPENDIX G: SPONSOR-PROPOSED ADVERSE EVENT LABELING

(b) (4)



Source: Gottlieb, KT, vedolizumab Crohn's disease BLA Clinical Review (2)

APPENDIX H: SERIOUS INFECTION INCIDENCE DENSITY IN VEDOLIZUMAB CLINICAL TRIALS

Time Adjusted Incidence Rates (per 1000 patient-years) of Infections in Patients With Moderate to Severe Inflammatory Bowel Disease – Overall Ulcerative Colitis and Crohn’s Disease Safety Population and HealthCore Integrated Research Database

Event, incidence rate (# events/1000 patients years)	HealthCore Integrated Research Database Moderate to Severe IBD		Vedolizumab Clinical Program	
	All Patients Rate (95% CI) N = 14733	TNF α Antagonist ^a N = 3348	VDZ ^b N = 2330	PBO/PBO N = 504
Tuberculosis	0.52 (0.17-1.21)	1.46	0.83	0.00
Histoplasmosis	0.21 (0.03-0.75)	0.87	0.00	0.00
<i>Clostridium. difficile</i> diarrhea/colitis	3.14 (2.12-4.49)	4.10	7.11	0.00
<i>Salmonella</i> sepsis	0.00 (0.00-0.38)	0.00	0.21	0.00
<i>Salmonella</i> gastroenteritis and related terms	0.10 (0.00-0.58)	0.29	1.25	4.67
Campylobacter gastroenteritis	0.00 (0.00-0.38)	0.00	2.71	0.00
Cytomegalovirus colitis	0.52 (0.17-1.21)	0.29	1.87	0.00
Viral meningitis	0.52 (0.17-1.21)	0.58	0.42	0.00
<i>Listeria</i> meningitis	0.00 (0.00-0.38)	0.00	0.21	0.00
Cryptosporidiosis	0.00 (0.00-0.38)	0.00	0.21	0.00

Abbreviations: CD = Crohn’s disease; CI = confidence interval; IBD = inflammatory bowel disease; PBO = placebo; TNF α = tumor necrosis factor alpha; UC = ulcerative colitis; VDZ = vedolizumab.

a Patients currently using TNF α antagonists.

b Includes patients from Studies C13002, C13004, C13006, C13007, C13008, and C13011.

Source: Takeda Advisory Committee Briefing Document, Table 8-24 (8)

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/s/

DAVID C SHIH
01/24/2014

SIMONE P PINHEIRO
01/24/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 5, 2014

TO: Kevin Bugin, M.S., R.A.C., Regulatory Project Manager
Laurie Muldowney, M.D., M.P.H., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA 125476

APPLICANT: Millennium Pharmaceuticals, Inc: A Takeda Oncology Company

DRUG: vedolizumab
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS:

- Adult Ulcerative Colitis (UC): vedolizumab is indicated 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 UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist.
- Adult Crohn's Disease (CD): vedolizumab is indicated for reducing signs and symptoms, inducing and maintaining clinical response and remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active CD who have had an

inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist.

CONSULTATION REQUEST DATE: July 15, 2013
INSPECTION SUMMARY GOAL DATE: February 20, 2014
DIVISION ACTION GOAL DATE: May 20, 2014
PDUFA DATE: May 20, 2014

I. BACKGROUND:

Vedolizumab (MLN0002) is a humanized monoclonal antibody that binds to the α 4B7 integrin which is expressed on discrete populations of leukocytes involved in gut mucosal immunity. The new drug antagonizes the migration of leukocytes into gastrointestinal (GI) mucosa and thus reduces pathological bowel inflammation. Because this product is selective to the GI mucosa, the sponsor postulates that the risk of Progressive Multifocal Leukoencephalopathy is lower than with some of the currently marketed products for this indication.

The review division requested inspection of the following three protocols that were submitted in support of this application:

1. Protocol C13006 entitled “A Phase 3, Randomized, Placebo-Controlled Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN002) in Patients with moderate to Severe Ulcerative Colitis”
2. Protocol C13007 entitled “A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Crohn’s Disease” and
3. Protocol C13011 entitled “A Phase 3 Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn’s Disease.”

Protocol C13006 was conducted from January 2009 to March 2012 as an international trial. This Phase 3 study was divided into two phases; induction and maintenance. The induction phase comprised patients who enrolled in Cohort 1 (randomized, blinded, placebo-controlled study drug assignment) and Cohort 2 (active open-label MLN0002 treatment). Patients enrolled in Cohort 1 were randomized 3:2 to receive either MLN0002 or placebo at Week 0 and Week 2. The analysis of the efficacy of MLN0002 for the induction of clinical response and remission included data from Cohort 1 only.

The primary efficacy assessment was the difference in the proportions of patients with clinical response at Week 6 in the Vedolizumab group versus the placebo group, defined as a 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.

After completing the Induction Phase, including the Week 6 pre-dose assessments, all patients continued on to the Maintenance Phase. Those who received MLN0002 in the Induction Phase and achieved clinical response at Week 6 were randomized 1:1:1 to receive MLN0002 every 4 weeks, MLN0002 every 8 weeks, or placebo for an additional 44 weeks. Patients who received MLN0002 in the induction phase but did not achieve clinical response at Week 6 continued to receive MLN0002 every 4 weeks during the Maintenance Phase. Patients who received placebo in the Induction Phase continued to receive placebo. To preserve the blind to study assignment, infusion during the Maintenance Phase occurred at 4-week intervals for all patients. The primary efficacy assessments were the differences in the proportions of patients with clinical remission at Week 52 in the Vedolizumab every 4 weeks versus placebo groups and Vedolizumab every 8 weeks versus placebo groups, defined as a complete Mayo score of ≤ 2 points and no individual subscore >1 point.

Protocol C13007 was similar in design to C13006, but studied subjects with Crohn's Disease and was conducted from December 2008 to May 2012. For the induction phase, the primary efficacy assessments were the differences in the proportions of patients with clinical remission at Week 6 and enhanced clinical response at Week 6 in the Vedolizumab group versus the placebo group. Clinical remission was defined as CDAI score ≤ 150 points and enhanced clinical response was defined as a ≥ 100 -point decrease in CDAI score from baseline (Week 0). For the maintenance phase, the primary efficacy assessment was the difference in the proportions of patients with clinical remission at Week 52 in the Vedolizumab Q4W versus placebo groups and Vedolizumab Q8W versus placebo groups, defined as CDAI score ≤ 150 points.

A total of 1115 patients were enrolled and dosed, of whom 368 patients were enrolled into Cohort 1 (ITT Population) and 747 patients were enrolled into Cohort 2. Within Cohort 1, a total of 148 patients were randomized to receive placebo and 220 patients were randomized to receive Vedolizumab. There were 747 patients enrolled into Cohort 2, each of whom received open-label Vedolizumab induction therapy and is included in the Induction Phase Safety Population. All patients who completed the Induction Phase entered the Maintenance Phase. Treatment assignments were based on the Induction Phase treatment and the investigator-assessed treatment response at Week 6. A total of 461 Vedolizumab patients had a clinical response during the Induction Phase, and were randomized to receive placebo (N = 153), Vedolizumab Q8W (N = 154), or Vedolizumab Q4W (N = 154) during the Maintenance Phase. Another 506 Vedolizumab patients did not respond during the Induction Phase, and were assigned to receive Vedolizumab Q4W during the Maintenance Phase. Patients in the Induction Study placebo treatment group (N = 148) continued to receive placebo during the Maintenance Phase.

Protocol C13011 was an induction trial only and required that subjects were randomized 1:1 to receive either 300 mg of vedolizumab or placebo I.V at Weeks 0, 2, and 6. The primary efficacy assessment was the difference in the proportion of patients who previously failed TNF α antagonist therapy who are in clinical remission at Week 6 (see definition above) in the

vedolizumab group vs. placebo group. Sustained Clinical Remission was defined as CDAI score of ≤ 150 points at Week 6 and Week 10. Sustained Enhanced Clinical Response was defined as a ≥ 100 point decrease in CDAI score from baseline (Week 0) at both Week 6 and Week 10, and Treatment Failure was defined as need for rescue medication or major surgical intervention for treatment of CD, or study drug-related adverse event leading to discontinuation of study drug .

II. RESULTS (by Site):

Type/Site # and Name of Inspected Entity	Protocol # / # of Subjects Randomized	Inspection Date	Final Classification
CI/Site # 04006 Gert Van Assche, M.D. UZ Leuven, Herestraat 49 Leuven, Belgium 3000	C13006/ 41 subjects C13007/ 32 subjects C13011/ 19 Subjects	October 21 to 29, 2013	NAI
CI/Site # 12019 Zdenka Zadorova, M.D. Fakultni nemocnice Kralovske Voinohrady Srobarova 50, Praha 10 Czech Republic 100 34	C13006/ 9 subjects C13007/ 9 subjects C13011/ 5 Subjects	November 4 to 11, 2013	NAI
CI/Site 58045 Scott Lee, M.D. University of Washington School of Medicine 1959 N.E. Pacific Avenue Box 356424 AA103 Seattle, WA 98195	C13006/ 15 subjects C13007/ 21 subjects C13011/ 18 Subjects	September 3 and October 3, 2013	VAI
CI/Site 58156 Seema Dar, M.D. Stone Oak Research Foundation 110 Stone Oak Loop, Suite 101 San Antonio, TX 78258	C13006/ 8 subjects C13007/ 3 subjects	October 7 to 15, 2013	NAI
Sponsor: Millennium: The Takeda Oncology Company 35 Landsdowne Street Cambridge, MA 02139	C13006 C13007 C13011 7 study sites reviewed	December 20 to 23, 2013	Pending* (preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Gert Van Assche, M.D.**UZ Leuven, Herestraat 49, Leuven, Belgium 3000**

- a. **What was inspected:** At this site, for Protocol C13006, a total of 49 subjects were screened, 41 were enrolled and 25 subjects discontinued from the study. An audit of 13 subjects' records was conducted. For Protocol C13007, a total number of 39 subjects were screened, 32 were enrolled and 24 subjects discontinued from the study. An audit of 10 subjects' records was conducted. For Protocol C13011, a total number of 23 subjects were screened, 19 were enrolled and 1 subject discontinued from the study. An audit of 19 subjects' records was conducted. The review included consent form documents, study correspondence, source records, hardcopy print outs of subject diary data entered into the IVRS system during the trials and the CD containing the CRFs.
- b. **General Observations/Commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

2. Zdenka Zadorova, M.D.**Praha 10, Czech Republic 100 34**

- a. **What was inspected:** At this site, for Protocol C13006, a total of 9 subjects were screened, 9 were enrolled and 7 subjects completed the study. An audit of 9 subjects' records was conducted. For Protocol C13007, a total number of 10 subjects were screened, 9 were enrolled and 9 subjects completed the study. An audit of 10 subjects' records was conducted. For Protocol C13011, a total number of 5 subjects were screened, 5 were enrolled and 5 subjects completed the study. An audit of 5 subjects' records was conducted. The review included consent form documents, study correspondence, source records, hardcopy print outs of subject diary data entered into the IVRS system during the trials and the CD containing the CRFs.

- b. **General observations/commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

3. Scott Lee, M.D.

University of Washington School of Medicine, Seattle, WA 98195

- a. **What was inspected:** At this site, for Protocol C13006, a total of 24 subjects were screened, 15 were enrolled and 5 subjects completed the study. An audit of 24 subjects' records was conducted. For Protocol C13007, a total number of 33 subjects were screened, 21 were enrolled and 5 subjects completed the study. An audit of 33 subjects' records was conducted. For Protocol C13011, a total of 26 subjects were screened, 18 subjects were enrolled and 18 subjects completed the study. An audit of 26 subjects' records was conducted. The inspection of this site included review of the consent form documents and procedures, clinical site operating procedures and documentation, subject source records, and case report forms. A comparison of source documents was made with the line listings from the BLA submission provided to the FDA field investigator.
- b. **General Observations/Commentary:** The adverse events were reported as specified in the protocol. The CDER data listings were compared with the source documents and no discrepancies were observed. The source was compared with the e-CRF data. No major transcription errors were observed. For the primary endpoints, the CDAI scores and Mayo scores were calculated centrally by the sponsor. The data elements comprising the scores (laboratory values, subject and physician assessments) were able to be verified at the site.

A Form FDA 483 was issued for the following violations and Dr. Lee adequately responded, as noted below, to the inspection findings in a letter dated October 23, 2013.

1. No phone calls were made to subjects who enrolled in protocols 13006 and 13007 and reported PML symptoms to reassure and instruct that they may remain in the study and to confirm that the symptoms have not recurred or persisted. In his response, the CI stated that the calls were made but not documented.
2. A stool sample for the analysis of the Fecal Calprotectin was not collected in 12 out of 24 subjects enrolled in Protocol 13006. In his response, the CI noted this lapse, due to difficulty for subjects to produce stool samples and promised increased communication with the sponsor to mitigate the issue if this type of problem should recur.

3. Pharmacist technician ^{(b) (6)} involved in the study drug reconstitution, dose preparation and dispensing is not included in the Site Personnel Signature/Delegation Log for Protocols C13006 and C13007. In his response, the CI attributed this to the blinded/unblinded nature of the IP logs and promised corrective action such that the site will not maintain two separate logs.
 4. For Protocol C13007, the CDAI scores were not calculated as specified in the protocol for 15 out of 21 subjects enrolled in the study. In his response, Dr. Lee attributed this to the fact that the site was using their usual guidelines for calculation of the CDAI and had not realized that the sponsor guideline differed from the site guideline.
- c. **Assessment of data integrity:** The violations noted above did not adversely affect data integrity or subject safety. The endpoints were calculated centrally by the sponsor as noted below. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Seema Dar, M.D.
Stone Oak Research Foundation, San Antonio, TX 78258

- a. **What was inspected:** At this site, for Protocol C13006, a total of 10 subjects were screened, 8 were enrolled and 4 subjects completed the study. An audit of 4 subjects' records was conducted. For Protocol C13007, a total number of 7 subjects were screened, 3 were enrolled and 3 subjects completed the study. An audit of 3 subjects' records was conducted. The review included consent form documents, study correspondence, source records, hardcopy print outs of subject diary data entered into the IVRS system during the trials and the CD containing the CRFs.
- b. **General Observations/Commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events, and the source data for the primary efficacy data were able to be verified at the site.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

5. Sponsor: Millennium: The Takeda Oncology Company
35 Landsdowne Street, Cambridge, MA 02139

Note: Observations below for this site are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon further review of the EIR.

- a. **What was inspected:** For the sponsor inspection, monitoring for seven study sites was reviewed. The inspection reviewed regulatory files for Protocols C13006, C13007 and C130011. This included monitoring procedures and reports for seven clinical sites as well as procedures and systems used to collect data and calculate the primary endpoints for each of the clinical trials.
- b. **General Observations/Commentary:** No regulatory violations were noted and a Form FDA 483 was not issued. The calculations for the CDAI and Mayo scores conducted by the sponsor were compared with the line listings submitted with the BLA and provided to the FDA investigator and no discrepancies were noted. The sponsor monitoring was adequate. One evidence for this was that, for Studies C13006 and C13007, Millennium noted problems early in the course of each study and took actions as follows:
The protocols required that the study sites use their own calculated CDAI and Mayo scores for subject care purposes and, in the case of Studies C13006 and C13007, the study site calculations also determined which subjects are randomized at Week 6 into the maintenance phase. The CDAI and Mayo scores at the end of each study were calculated centrally. In June of 2009, approximately six months after the first subjects were enrolled in each of the studies, during quarterly review of the data, Millennium noted discrepancies in the data. Millennium determined that study sites were not calculating the CDAI and Mayo scores correctly, resulting in some subjects being categorized incorrectly as responders or nonresponders. This “miscategorization” by the study sites resulted in some subjects being assigned into the incorrect arm for the maintenance study. For Study C13006, this occurred in 59 of 895 enrolled subjects. For Study C13007, this occurred in 107 of 1116 enrolled subjects. This “miscategorization” is described in detail in Sections 11.2.1-M of each report, “Primary Efficacy Endpoint, Maintenance.”
After discovering the miscalculations, Millennium took action by requesting that (b) (4), the study monitor, improve the review of the CDAI and Mayo scores. Millennium also conducted re-training for (b) (4) and their clinical research associates and updated the monitoring plan to include a more in depth overview and review of the CDAI and Mayo score calculations. In addition, Millennium created an in-depth Data Quality Initiative for the Gemini Program (which includes Studies C13006 and C13007). Within the Data Quality Initiative program, Millennium provided detailed instructions to (b) (4) to assure better monitoring, including closer review of primary endpoints (CDAI and Mayo calculations included).
- Reviewer note: The sponsor was not cited because they identified the problem, took corrective action and reported the occurrence in the clinical study reports. For an example of this occurrence, see the findings at the Lee site.*
- c. **Assessment of data integrity:** The clinical study reports accurately reflect the conduct of the studies, including the miscalculations of the CDAI and Mayo scores that occurred at some study sites early in the trials for Studies C13006 and C13007. The

studies appear to have been conducted adequately, and the data generated by the sponsor appear acceptable in support of the respective indications.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigators and the sponsor were inspected for this application. Three of the clinical sites, Drs. Van Assche, Zadorova, and Dar were classified as NAI and Dr. Lee's site was classified as VAI for observations that did not significantly impact data reliability or subject safety. The sponsor inspection has a preliminary classification of NAI with the findings noted above and described in the study reports for Studies C13006 and C13007. The data from these studies is considered reliable in support of the application.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR from the sponsor inspection.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
02/10/2014

KASSA AYALEW
02/10/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

M E M O R A N D U M

From: Erica L. Wynn, MD, MPH Medical Officer
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Associate Director,
Pediatric and Maternal Health Staff (PMHS)

To: Division of Gastroenterology and Inborn Error
Products (DGIEP)

BLA(s): 125476 and 125507

Drug: Vedolizumab (Entyvio®)

Sponsor: Takeda Pharmaceuticals U.S.A., Inc.

Approved indications: None

Proposed indications: 1) 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 (TNF-alpha) antagonist.

2) 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 (TNF α) antagonist.

Consult Question:

PMHS was asked to attend team meetings for this efficacy supplement to the BLA and assist with preparation of the Pediatric Review Committee (PeRC) paperwork.

Materials Reviewed

- PMHS consult request dated June 28, 2013 (DARRTS Reference ID: 3338094)
- Sponsor's Request for Deferral of Pediatric Studies submitted with application
- Sponsor's Request for Waiver of Pediatric Studies submitted with application
- Sponsor's Proposed labeling for Vedolizumab
- Approval letter for BLA 125104 Natalizumab (Tysabri®)
- Deferral Extension letter for BLA 125104 Natalizumab (Tysabri®)
- EMA Opinion of the Paediatric Committee on the Agreement of a Pediatric Investigation Plan and a Deferral and a Waiver
- EMA Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan.

Background and Relevant Regulatory History:

Vedolizumab

On June 20, 2013, Takeda submitted Biologics License Application (BLA) 125476 for vedolizumab (Entyvio®), a new molecular entity, which is proposed for use in adults with moderately to severely active Crohn's Disease (CD) or Ulcerative Colitis (UC). For administrative purposes, this BLA was divided into two applications (one for each of the proposed indications). BLA 125476 for Ulcerative Colitis (UC) has been given priority review designation. BLA 125507, submitted August 19, 2013, is the clone BLA application for the Crohn's Disease indication and has been designated for standard review.

Vedolizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against the human lymphocyte integrin $\alpha_4\beta_7$. The drug product is available as a sterile lyophilized formulation in a single use vial providing 300mg of vedolizumab. After reconstitution with sterile water for injection to a concentration of (b) (4), the resulting solution is diluted into 250ml of normal saline for infusion. According to the sponsor, vedolizumab binds exclusively to $\alpha_4\beta_7$ integrin, a key mediator of gastrointestinal inflammation expressed on the surface of a subset of memory T

lymphocytes. By binding to $\alpha_4\beta_7$ integrin, vedolizumab selectively inhibits adhesion of T lymphocytes to mucosal addressin cell adhesion molecule-1(MAdCAM-1).

The proposed mechanism of action for vedolizumab is similar to the mechanism of action for natalizumab (Tysabri®, approved 2004, BLA 125104). During the clinical development of natalizumab, cases of progressive multifocal leukoencephalopathy (PML) emerged. Recognition of the PML risk resulted in the need for a risk mitigation program. Although no cases of PML have been observed thus far in the vedolizumab clinical development program, there is concern about the potential risk of PML because of the similar mechanisms of action for vedolizumab and natalizumab. This safety issue was one of the issues presented on December 9, 2013, to a Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. In a 21 (yes) to 0 (no) vote, the committee agreed that the applicant had adequately characterized the potential risk of PML with vedolizumab during the pre-marketing clinical development program. However, members also noted that continued monitoring and observation were still required.

Inflammatory Bowel Disease

Ulcerative Colitis (UC) and Crohn's Disease (CD) are forms of chronic idiopathic 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. A third form of inflammatory bowel disease, indeterminate colitis, is a diagnosis of exclusion (in both pediatric and adult patients) when confirmation of UC or CD cannot be made based on standard clinical testing, including colonoscopy, imaging, laboratory tests, and biopsy.^{3,5} Clinically, many patients with indeterminate colitis evolve to a definite diagnosis of UC or CD on follow-up.¹ The exact cause of IBD is unknown, however the etiology is likely a combination of genetic, environmental and infectious factors. The distinction between UC and CD has implications, not limited to the choice of medical treatment and/or surgery, disease course and prognosis.¹

Population based studies suggest that IBD is unevenly distributed throughout the world, with the highest disease rates occurring in Westernized countries.² Studies from Great Britain suggest that the incidence of IBD in children and adolescents has increased over the last decades.³ CD (also known as regional enteritis) affects both pediatric and adult patients, however most ambulatory care visits for the disease occurs among young and middle-aged adults.⁴ A study by S. Kugathasan and colleagues measured the incidence of pediatric IBD in Wisconsin, and determined that the age-related annual incidence of new-onset pediatric CD was negligible in children less than 6 years of age.⁵ In contrast, UC is believed to be more common in younger pediatric patients.⁶ However, despite the more common prevalence of UC in younger pediatric patients, the US incidence of UC in children 4 years of age and younger is still very low, with the annual incidence in this age group ranging between 0.2-0.7 per 100,000.^{5,6} The prevalence of indeterminate colitis appears to be a function of age (decreasing as the age of the child increases). A small retrospective database analysis by Carvalho and colleagues in 2006, showed that patients

with indeterminate colitis had a significantly younger mean age at diagnosis compared with patients with CD but not compared with patients with UC.⁷ The analysis also showed that 33.7% of patients with an initial diagnosis of indeterminate colitis were reclassified to either CD or UC after a median follow-up of 1.9 years (range 0.6-4.5 years).⁷

Discussion of Sponsor's Pediatric Plan:

Vedolizumab is a new molecular entity being proposed for use in adult patients with Ulcerative Colitis and Crohn's Disease. Under PREA, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. Products that have been granted orphan designation for a particular indication in a population are exempt from PREA requirements. The applicants for the vedolizumab product have not requested orphan designation. Because vedolizumab is a new molecular entity, PREA is triggered. The sponsor submitted a request to defer pediatric studies required under PREA for both the CD and UC indications in patients older than (b) (4). The reason for the deferral was that "adult studies completed" and the product is "ready for approval". The sponsor has requested a partial waiver in patients (b) (4) of age for both UC and CD on the grounds that studies are impossible or highly impracticable (because the number of pediatric patients is so small or geographically dispersed). To support their request, the sponsor provided epidemiological data. The sponsor also argued that there is a high rate of indeterminate colitis in pediatric patients less than (b) (4) of age and that there is no validated efficacy scoring system for indeterminate colitis.

Regulatory Standards for Full and Partial Waiver of PREA requests

FDA may grant a full or partial waiver for the requirement to submit pediatric assessments required under the Pediatric Research and Equity Act (PREA), if the applicant certifies and FDA finds evidence of one or more of the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed) (section 505B(a)(4)(B)(i) of the Act)
2. There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group (section 505B(a)(4)(B)(ii) of the Act). If a partial waiver is granted based on evidence that the drug is unsafe or ineffective in pediatric populations, the applicant must include this information in the labeling for the drug or biological product (section 505B(a)(4)(D) of the Act).
3. The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group AND is not likely to be used by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

Additionally FDA may grant a partial waiver if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for an age group have failed

(section 505B(a)(4)(B)(iv) of the Act). If a partial waiver is granted on the basis that it is not possible to develop a pediatric formulation, the partial waiver shall cover only the pediatric groups requiring that formulation (section 505B(a)(4)(C) of the Act). The information on the sponsor's attempts to produce an appropriate pediatric formulation will be posted publically on the FDA website.

Reviewer Comment:

The sponsor's request for a partial waiver on the grounds that studies are "not feasible" in pediatric patients (b) (4) and younger appears reasonable. Furthermore, PMHS believes the epidemiologic data and prior experience with IBD products more appropriately supports a partial waiver in pediatric patients < 5 years with UC and pediatric patients < 6 years with CD which is consistent for other UC and CD products recently reviewed by the PeRC. No studies of IBD prevalence in the United States have been published using data published after 2007 and therefore current time trends remain unknown.⁸ However, prior epidemiologic data suggest that there is a high incidence of indeterminate colitis in younger patients and the small number of pediatric patients with UC and CD below the aforementioned cut-offs may preclude enrolling sufficient patient numbers to provide useful data.

Based on review of the medical literature and PREA requirements for other products used to treat IBD, the difference in the age cut-offs for partial waivers in Crohn's Disease (age 6 years) and Ulcerative Colitis (age 5 years) is not entirely clear. The Division may consider harmonizing the age requirements for PREA studies to less than 6 years of age if the Division finds no reason to continue the difference moving forward or if sponsors with current PREA requirements have difficulty completing their studies in a timely fashion.

Ulcerative Colitis

In most studies, the incidence of Ulcerative Colitis peaks between adolescence and early adulthood (i.e. people aged 15-30 years).⁹ UC occurs less frequently in children younger than 5 years of age.⁹ Partial waivers for mesalamine-based products used in UC have been granted for pediatric patients less than 5 years of age [Asacol® (mesalamine), NDA 19651]. Similarly, Written Requests for other mesalamine-based products used in UC have excluded children younger than 5 years of age (Asacol® NDA 19651; Canasa® IND 63621; Lialda® NDA 22000; and Pentasa®, NDA 20049). Moreover, the one completed program in UC (Asacol) enrolled only one patient in the 5-8 year age group. Other products for pediatric UC [e.g. golimumab, BLA 125289 and Giazo® (balsalazide disodium), NDA 022205] have received orphan designation, thus PREA did not apply. Notably, although Giazo® received orphan designation, another balsalazide disodium product, Colazal is labeled for use in patients 5 years and older with mildly to moderately active ulcerative colitis.

Crohn's Disease

With respect to CD, the disease most commonly starts in patients between the ages of 13 and 30.¹⁰ Although children and adolescents can be diagnosed at any age, the second decade of life is the most common period.¹¹ Other products used to treat moderate to

severe CD have received partial waivers to study pediatric patients less than 6 years of age [Humira® (adalimumab)BLA 125057 and Remicade® (infliximab) BLA 103772]. (Note: Remicade is approved for pediatric patients 6 years and older with moderately to severely active Crohn's Disease.) Given the rate of indeterminate colitis, and the Division's precedent, waiving PREA-required trials in pediatric patients less than 6 years of age would be reasonable. A partial waiver in this age group would also be consistent with PREA requirements for Tysabri, another alpha-integrin approved for use in adults with CD. Additional data were required to assess a specific safety concern of progressive multifocal leukoencephalopathy (PML) prior to the initiation of deferred pediatric trials using Tysabri in pediatric patents ages 6 to 17 years of age. Although there have been no cases of PML noted during the pre-marketing clinical development plan for vedolizumab, if cases of PML emerge or if the Division remains concerned about an increased risk of PML, a full waiver for safety could be considered and granted at the Division's discretion. Notably, if pediatric studies are allowed to progress, a step-wise approach similar to that taken with Tysabri seems prudent.

Conclusion:

PMHS participated in the filing, mid-cycle and wrap-up meetings and assisted DGIEP with the review of the paperwork needed for the Pediatric Review Committee (PeRC) Meeting on January 8, 2014. PeRC agreed that partial waivers to study pediatric patients less than 6 years of age with moderate to severe Crohn's and patients less than 5 years of age with moderate to severe Ulcerative Colitis are appropriate. PeRC also agreed that pediatric studies can be deferred for all remaining age groups in each respective indication.

References

- ¹ Guindi, M and Riddell RH. "Indeterminate Colitis" *Journal of Clinical Pathology*. 2004;57:1233-1244.
- ² Lashner, BA. "Epidemiology of Inflammatory Bowel Disease." *Gastroenterology Clinics of North America*. 1995;24:467-474.
- ³ Sawczenko, A, Sandhu BK, Logan RF, Jenkins H, Taylor CJ, Mian S, et.al. "Prospective survey of childhood inflammatory bowel disease in the British Isles." *Lancet*.2001;357:1093-1094.
- ⁴ Everhart, JE. Chapter 19: Inflammatory Bowel Disease. In:] Everhart JE, editor. The burden of digestive diseases in the United States. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office, 2008; NIH Publication No. 09-6443 [pp.97].
- ⁵ Kugathasan S., Judd RH, Hoffman RG, Heikenen J, Telega G, Khan F, et al., "Epidemiologic and Clinical Characteristics of Children with Newly Diagnosed Inflammatory Bowel Disease in Wisconsin: A Statewide Population-Based Study" *The Journal of Pediatrics*.2003;143(4): 525-531.
- ⁶ Heyman MB, Kirschner BS, Gold BD, Ferry G, Baldassano R, Cohen SA, et al. "Children with early-onset inflammatory bowel disease (IBD); analysis of a pediatric IBD consortium registry. *Journal of Pediatrics*.2005;146(1):35-30
- ⁷ Carvalho RS, Abadom V, Dilworth HP, Thompson R, Oliva-Hemker M, Cuffari C. "Indeterminate Colitis: a significant subgroup of pediatric IBD." *Inflammatory Bowel Disease*. 2006;12(4):258-262.
- ⁸ Kappelman MD, Moore KR, Allen JK, and Cook SF. "Recent Trends in the Prevalence of Crohn's Disease and Ulcerative Colitis in a Commercially Insured US Population." *Digestive Diseases and Science*. 2013;58;519-525.
- ⁹ Kelsen JR, Mamula P, Cuffari C. et.al.;. "Ulcerative Colitis in Children". Updated October 24, 2013. Accessed from Medscape. Available at <http://emedicine.medscape.com/article/930146-overview#a0101>
- ¹⁰ Sauer CG, Kugathasan S. "Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD." *Gastroenterology Clinics of North America*. 2009;38(4):611-628.
- ¹¹ Day AS, Ledder O, Leach ST, and Lemberg. "Crohn's and colitis in children and adolescents." *World Journal of Gastroenterology*.2012;18(41):5862-5869.

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/s/

ERICA WYNN
01/23/2014

HARI C SACHS
01/24/2014

LYNNE P YAO
01/29/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: December 19, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: ENTYVIO (vedolizumab)

BLA: 125476/125507

Subject: Labeling recommendations for subsections 8.1, 8.2 and 8.3

Applicant: Takeda

Materials Reviewed: Sponsor's initial labeling submitted June 20, 2013

Consult Question: Please provide labeling recommendations for subsections 8.1, 8.2 and 8.3

INTRODUCTION

On June 20, 2013, Takeda submitted BLA 125476 for ENTYVIO (vedolizumab), a new molecular entity (NME), for the treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD). The Division decided an administrative split was appropriate for this BLA. BLA 125476 has been designated a priority review for the ulcerative colitis indication and BLA 125507 has been designated a standard review for the Crohn's disease indication.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Vedolizumab labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Vedolizumab

Vedolizumab is a monoclonal antibody that belongs to the integrin receptor antagonist class of drugs.¹ Vedolizumab binds to human $\alpha 4\beta 7$ integrin inhibiting mucosal addressin cell adhesion molecule (MAdCAM 1). The $\alpha 4\beta 7$ integrin is expressed on the surface of memory T-lymphocytes that migrate into the gastrointestinal tract and participate in inflammatory processes leading to ulcerative colitis and Crohn's disease.²

Inflammatory Bowel Disease (IBD)

Ulcerative colitis and Crohn's disease are both inflammatory bowel diseases. Ulcerative colitis and Crohn's disease both usually develop between the ages of 15 and 30, and thus, both diseases occur in females of reproductive potential.³ Ulcerative colitis is more common than Crohn's disease and affects the mucosa of the colon causing inflammation of the digestive system. Symptoms can include rectal bleeding, abdominal cramping, fatigue, weight loss and can cause serious complications such as rupture and toxic megacolon.^{3,4} Crohn's disease affects the ileum or small intestine most commonly.⁴ Symptoms include rectal bleeding, abdominal pain and diarrhea.⁴

¹ Muldowney, L. Clinical Review. November 20, 2013.

² Feagan, B., Rutgeerts, P., Sands, B., Hanauer, S., Colombel, J., Sandborn, W., Assche, G. (2013). Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *The New England Journal of Medicine*, 369(8); 699-710.

³ Ulcerative Colitis. U.S., Department of Health and Human Services. National Digestive Diseases Information Clearinghouse (NDDIC). www.digestive.niddk.nih.gov/ddiseases/pubs/colitis/. Accessed 3 December 2013.

⁴ Crohn's Disease. Department of Health and Human Services. National Digestive Diseases Information Clearinghouse (NDDIC). www.digestive.niddk.nih.gov/ddiseases/pubs/crohns/index.aspx. Accessed 3 December 2013.

IBD and Pregnancy

Approximately 25% of women with IBD will become pregnant and two-thirds of these women have active disease during pregnancy.⁵ It is important to counsel female patients with IBD who wish to become pregnant or who are pregnant about treatment options during pregnancy and adverse pregnancy outcomes. Patients with active disease during the time of conception have shown to have higher rates of negative pregnancy outcomes such as, spontaneous abortion, low birth weight (LBW) and preterm birth.⁶ However, when conception occurs during a period of disease inactivity rates of adverse pregnancy outcomes were much lower.⁶ In addition, often an exacerbation of disease has been seen, mainly in the first trimester, upon discontinuation of drug therapy.⁶

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The Drugs and Lactation Database (LactMed)⁷ was searched for available lactation data on with the use of vedolizumab and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

⁵ Pedersen, N., Bortoli, A., Duricova, D., D’Inca, R., Panelli, M., Gisbert, J., et al. (2013). The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. *Aliment Pharmacol Ther*, 38:501-512.

⁶ Vermeire, S., Carbonnel, F., Coulie, P., Geenen, V., Hazes, J., Masson, P., et al. (2012). Management of inflammatory bowel disease in pregnancy. *Journal of Crohn’s and Colitis*, 6; 811-823.

⁷ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

Pregnancy Exposure Data

New drugs like vedolizumab generally have little or no human pregnancy experience prior to approval, unless the drug is specifically indicated for a pregnancy-related condition and obtaining human pregnancy data to adequately inform product labeling is important for all drug and biological products. Thus, collection of drug safety data on use during human pregnancy is often performed post-approval. The Food and Drugs Administration Amendments Act (FDAAA) of 2007 (see PL 110-85, Title IX, sec 905(a)(3)(C)(iv)) recommended complementary approaches to gather and analyze postmarketing data and information to assess the safety of use of a drug in domestic populations (such as in pregnant women) that were not included or underrepresented in the clinical trials used to approve a drug.

Options for collecting meaningful pregnancy exposure data include the establishment of a drug-based prospective cohort study (pregnancy exposure registry), collaboration with an established disease-based pregnancy exposure study, or enhanced pharmacovigilance with either an established pregnancy surveillance program or reporting and follow-up on known pregnancy exposures.

In 2002, FDA published, “Guidance for Industry on Establishing Pregnancy Exposure Registries.”⁸ In this guidance, a pregnancy exposure registry is defined as a prospective observational study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes and is one method of collecting data on drug exposure during pregnancy before pregnancy outcomes are well established. Pregnancy exposure registries proceed from the point of drug exposure and pregnant women are enrolled before the outcome of pregnancy is known. Drugs or biological products that are considered good candidates for pregnancy exposure registries include those that have a high likelihood of use by women of childbearing potential. Pregnancy exposure registries are unlikely to be required when the product is not used or rarely used by women of childbearing potential. The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. In order to collect meaningful data, the size of a pregnancy exposure registry should be large enough to either detect a difference or show no difference between the exposed and control groups. An internal and/or external (in certain situations) control group is required for pregnancy exposure registries.

The Organization of Teratology Information Specialists (OTIS) has established the *Autoimmune Diseases in Pregnancy Study* which studies the possible effects of autoimmune diseases (such as multiple sclerosis, Crohn’s Disease, rheumatoid arthritis, psoriatic arthritis, and psoriasis) and the drugs used to treat these conditions can have on pregnancy.⁹ Numerous sponsors of FDA-approved drugs for autoimmune diseases collaborate with this OTIS study.

Enhanced pharmacovigilance can involve the establishment of a pregnancy surveillance program that is set up much like a pregnancy exposure registry; however, there are no control groups and data may be collected both prospectively and retrospectively. Additionally, enhanced pharmacovigilance may include the sponsor reporting pregnancy exposures with follow-up on all

⁸ See Guidance for Industry: Establishing Pregnancy Exposure Registries, August 2002

⁹ <http://www.pregnacystudies.org/ongoing-pregnancy-studies/autoimmune-studies/>

reports. This last strategy is usually reserved for products rarely prescribed in females of reproductive potential.

Annual interim pregnancy exposure reports for pregnancy registries or enhanced pharmacovigilance programs are generally submitted to FDA on an agreed upon schedule until FDA has acknowledged that sufficient data have been collected. Information on established drug-based or disease-based pregnancy exposure programs should be placed prominently in the pregnancy subsection of labeling to inform prescribers and patients that a pregnancy exposure registry is in existence.

Drugs and Lactation

The American Academy of Pediatrics (AAP) recommends that all mothers who are able to breast-feed should do so until their infant reaches 1 year of age because the AAP considers breast-feeding to be the ideal method of feeding and nurturing infants.¹⁰ Furthermore, breast-feeding is the most complete form of nutrition for infants and offers a range of health benefits for both mothers and breast-feeding infants.¹⁰ Women make decisions about drug treatment and the continuation of lactation in the absence of data, and thus, women may choose to discontinue breast-feeding unnecessarily.

Many, but not all, drugs transfer to breast milk. The transport of a drug into breast milk is largely a function of the drug's physicochemical properties and its concentration in maternal plasma. All of the following factors influence the amount of drug transfer into human milk: plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways. Factors that tend to produce higher human milk levels of drugs include: higher maternal plasma concentration, higher lipid solubility, higher pK_a, lower protein binding, and lower molecular weight.¹¹ The mean pH of human milk is 7.2, about 0.2 units lower than that of plasma.^{11,12} This difference influences the transfer of drugs into milk, more so for drugs that are weak bases with pK_a values in that range. Drugs with higher molecular weights, especially those with weights greater than 800 Daltons, must generally be actively transported or dissolved in the cells lipid membranes. Most drugs move between maternal serum and human milk based on equilibrium forces. However, a few drugs enter human milk by active transport. Not all drug transport systems in the breast have been identified. Drugs that are more lipid soluble may accumulate in the lipid fraction of the milk, leading to higher concentrations of drug in human milk than in maternal plasma.¹¹

Clinical lactation data should be available for drugs that are likely to be used in females of reproductive potential unless the drug has a known or potential serious safety concern that would preclude collection of such data. Nursing mothers labeling should adequately inform the use of a drug during lactation. Clinical lactation studies can be designed to assess the extent of drug into breast milk and the daily infant dose through breast milk; the severity and frequency of adverse events in breast-fed infants exposed to maternal drug through breast milk, and potential effects on milk production.

¹⁰ The AAP Section on Breastfeeding, 2005

¹¹ Hale, T. (2012). Medications and Mother's Milk. Amarillo, TX: Edwards Brothers Malloy.

¹² Morriss, F., Brewer, E., Spedale, S., Riddle, L., Temple, D., Caprioli, R., et al. (1986). Relationship of Human Milk pH During Course of Lactation to Concentrations of Citrate and Fatty Acids. *Pediatrics*, 78 (3); 458-464.

CONCLUSION

PMHS-MHT recommends a post-marketing requirement (PMR) for the collection of pregnancy exposure data in order to assess the safety of use of vedolizumab in pregnant women as this population was not represented in pre-marketing clinical trials and the drug will likely be used in females of reproductive potential. PMHS-MHT recommends that the sponsor consider fulfilling this PMR by establishing a drug-based pregnancy exposure program (pregnancy exposure registry or pregnancy surveillance program) or collaborating with an existing disease-based pregnancy exposure study such as the OTIS *Autoimmune Diseases in Pregnancy Study*. The method of data collection should be based on the ability and feasibility to collect meaningful data. The pregnancy subsection of vedolizumab labeling should include contact information for established drug- or disease-based pregnancy exposure programs.

PMHS-MHT recommends a post marketing commitment (PMC) for a milk-only clinical lactation study using a validated assay conducted in lactating women who are using vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk in order to appropriately inform the Nursing Mother's subsection of labeling.

The pregnancy subsection of the labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations.

PMHS-MHT discussed our labeling recommendations with DGIEP at a meeting on October 24, 2013. PMHS-MHT and the DGIEP Pharmacology/Toxicology team recommendations are below and reflect the discussions with the Division at that meeting.

PMHS-MHT refers to the final BLA action for final labeling.

SPONSORS LABELING RECOMMENDATIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

(b) (4)

(b) (4)

8.3 Nursing Mothers

(b) (4)

17 Patient Counseling Information

(b) (4)

Reviewer comment: PMHS-MHT recommends deleting the (b) (4) from section 17 (b) (4)

(b) (4)

PMHS LABELING RECOMMENDATIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category B

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. (b) (4)

(b) (4)

Reviewer comment: The language above should be added if a pregnancy exposure registry is established.

Risk Summary

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

(b) (4)

Animal Data

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

8.3 Nursing Mothers

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

Reviewer comment: PMHS-MHT refers to final BLA action for final labeling language.

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/s/

CARRIE M CERESA
12/19/2013

JEANINE A BEST
12/19/2013

LYNNE P YAO
12/20/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: November 26, 2013

Reviewer: Lisa Vo Khosla, PharmD, M.H.A.
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, M.S., PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Entyvio (Vedolizumab)
Powder for Injection,
300 mg per vial

Application Type/Number: BLA #125476

Applicant/sponsor: Millenium Pharmaceuticals, Inc.

OSE RCM #: 2013-1621

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

As part of the approval of Entyvio (Vedolizumab), the Division of Gastroenterology and Inborn Error Products (DGEIP) requested we review the proposed container labels, carton labeling, and Full Prescribing Information for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the June 20, 2013 BLA 125476 submission:

- Active Ingredient: Vedolizumab
- Indication of Use: Crohn's disease and ulcerative colitis
- Route of Administration: Intravenous infusion
- Dosage Form: Sterile powder for injection
- Strength: 300 mg/vial
- Dose and Frequency: 300 mg IV infusion over 30 minutes at weeks 0, 2, and 6, then 8 weeks thereafter (b) (4)
- How Supplied: 20 mL single-use vial individually packaged inside a cardboard carton.
- Storage: Refrigeration (2°C to 8°C)

1.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 20, 2013 (Appendix B)
- Carton Labeling submitted June 20, 2013 (Appendix C)
- Full Prescribing Information submitted June 20, 2013 (Appendix D)

¹ Institute for Healthcare Improvement (IHI). Failure modes and effects analysis (FMEA) [Internet]. Cambridge: IHI; c2013 [cited 2013 Oct 15]. Available from: <http://www.ihl.org/knowledge/Pages/Tools/FailureModesandEffectsAnalysisTool.aspx>

2 MEDICATION ERROR RISK ASSESSMENT

Vedolizumab is a new biologic product, indicated for the treatment of crohn’s disease (CD) and ulcerative colitis (UC). Although, the proposed product has a different mechanism of action from other biologics used to treat UC or CD, its dosage form (powder for injection) is similar to other currently marketed biologic products, such as Remicade (infliximab) and Benlysta (belimumab).

Therefore, we performed a risk assessment of the proposed full prescribing information to identify deficiencies that may lead to medication errors. We noted that the handling and preparation instructions were unclear, lacking specific details in some steps. We noted that the instructions did not describe clearly when to not administer or discard the product. Additionally, the administration instructions did not identify the infusion set to be used with this product. Thus, we provide recommendations in Section 4 to address these deficiencies.

Additionally, we reviewed the proposed container label and carton labeling to identify areas of improvement. We provide label and labeling recommendations in section 4 to increase prominence of important information to ensure safe use of the product.

3 CONCLUSIONS

We conclude that the proposed container label, carton labeling, and Full Prescribing Information can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4 RECOMMENDATIONS

A. Comments to the Division

Based on this review, we have made revisions to the Full Prescribing Information for review and consideration by DGEIP. See Appendix D for details.

B. Comments to the Applicant

DMEPA recommends the following be implemented prior to approval of this BLA:

1. Container Label and Carton Labeling

- a. Decrease the size of the symbol that appears next to the proprietary name and relocate it away from the proprietary name. As currently displayed, the symbol is too prominent and competes with the proprietary name. Additionally, the symbol may be interpreted as part of the proprietary name.
- b. Revise the font color of the proper name to provide better contrast against the white background. As currently presented, it is difficult to read the established name against the white background.
- c. Consider adding the dosage form on the line below the proper name, “vedolizumab”.

- d. Relocate the statement “Discard unused portion” from the side panel of the container label to appear with the statement “Single Use Vial” on the Principal Display Panel such that it is consistent with the carton labeling (i.e. “Single-Use Vial-Discard unused portion”)

If you have further questions or need clarifications, please contact Phong Do, OSE project manager, at 301-796-4795.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LISA V KHOSLA
11/26/2013

LUBNA A MERCHANT
11/26/2013

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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 25, 2013

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Error Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm. D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ENTYVIO (vedolizumab)

Dosage Form and Route: lyophilized powder for injection, for intravenous infusion

Application Type/Number: BLA 125476 & BLA 125507

Applicant: Takeda Pharmaceuticals U.S.A., Inc.

1 INTRODUCTION

On March 27, 2013, Takeda Pharmaceuticals U.S.A., Inc. (Takeda) submitted for the Agency's review the first portion of a rolling submission for Biologics License Application (BLA) 125476 for ENTYVIO (vedolizumab) lyophilized powder for injection, for intravenous use infusion. Takeda submitted the second portion of rolling BLA 125476 on April 8, 2013, and the third and final portion of the rolling BLA was submitted on June 20, 2013.

The proposed indication for ENTYVIO (vedolizumab) is 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 (TNF α) antagonist.
- 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 (TNF α) antagonist.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on July 9, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ENTYVIO (vedolizumab).

2 MATERIAL REVIEWED

- Draft ENTYVIO (vedolizumab) MG received on June 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 7, 2013.
- Draft ENTYVIO (vedolizumab) Prescribing Information (PI) received on June 20, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 7, 2013.
- Approved TYSABRI (natalizumab), comparator labeling dated May 24, 2013.
- Approved REMICADE (infliximab), comparator labeling dated November 6, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
11/25/2013

ADEWALE A ADELEYE
11/25/2013

LASHAWN M GRIFFITHS
11/25/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products

FINAL CARTON AND CONTAINER REVIEW

Date: 11/20/13
Reviewer: Rashmi Rawat, Ph.D.
Acting Team Leader,
Office of Biotechnology Products,
Division of Monoclonal Antibodies

Through: Sarah Kennett, Ph.D.
Review Chief,
Office of Biotechnology Products
Division of Monoclonal Antibodies

Kathleen Clouse, Ph.D.
Division Director,
Office of Biotechnology Products
Division of Monoclonal Antibodies

Application: BLA 125476

Product: Entyvio (vedolizumab)

Applicant: Takeda Pharmaceuticals U.S.A., Inc.

Submission Date(s): June 20, 2013, Nov. 11, 2013

Executive Summary

The carton and container labels for Entyvio (vedolizumab) were reviewed and found not to comply with one or more of the following regulations: 21 CFR 610.60 and 21 CFR 610.61; and the United States Pharmacopeia, 5/1/13-12/31/13, USP 36/NF 31. Labeling deficiencies were identified and communicated to the sponsor in an information request (IR) letter. The sponsor responded to the IR and submitted the revised label on 11/11/13. The revised carton and container labels submitted on Nov.11, 2013 comply with the regulations and are acceptable.

Background and Summary Description

Entyvio (vedolizumab) is indicated for the treatment of patients with moderately to severely active ulcerative colitis and moderately to severely active Crohn's disease. The product is supplied as a lyophilized cake in sterile single-use vials containing 300 mg of vedolizumab for intravenous use.

Materials Reviewed:



Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. **Conforms**

(2) The name, address, and license number of manufacturer; **Does not conform.** Manufacturer listed as [REDACTED]^{(b) (4)}.

***Reviewer's Comment:** In response to our IR, the sponsor revised the label and replaced [REDACTED]^{(b) (4)} with 'Manufactured by' to comply with the regulation.
The revised label is acceptable.*

(3) The lot number or other lot identification; **Conforms**

(4) The expiration date; **Conforms**

(5) The recommended individual dose, for multiple dose containers. **Not applicable.** This product is supplied in a single-dose vial.

(6) The statement: "Rx only" for prescription biologicals.
Conforms

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. **This conforms to the regulation.** A statement is provided in the carton label.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. **Not applicable**

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. **Not applicable**

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the

container is placed in a package which bears all the items required for a package label. **Not applicable**

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. **This could not be verified from the information provided.**

***Reviewer's Comment:** The sponsor was asked to provide this information in an information request dated 11/05/13. In response to our IR the sponsor provided a picture of the labeled container to demonstrate that the label allows the inspection of the contents of the container. The sponsor's response is acceptable.*

- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; **Conforms**
- C. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**
- D. 21 CFR 201.6 Drugs; misleading statements; **Conforms**
- E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] **Conforms**
- F. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**
- G. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**
- H. 21 CFR 201.25 Bar code; **Conforms**
- I. 21 CFR 201.50 Statement of identity; **Conforms**
- J. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms.**
- K. 21 CFR 201.55 Statement of dosage; **Conforms**
- L. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Start of Sponsor Material

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] **Conforms**

b) The name, addresses, and license number of manufacturer;
Does not conform. Manufacturer (b) (4).

Reviewer's Comment: In response to our IR, the sponsor revised the label and replaced (b) (4) with 'Manufacturer' to comply with the regulation. The revised label is acceptable.

c) The lot number or other lot identification; **Conforms**

- d) The expiration date; **Conforms**
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”. **Conforms**
- f) The number of containers, if more than one; **Not applicable**
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **Conforms**
- h) The recommended storage temperature; **Conforms**
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; **Conforms**
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; **Not applicable**
- k) The route of administration recommended, or reference to such directions in an enclosed circular; **Conforms**
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; **Not applicable.**
- m) The type and calculated amount of antibiotics added during manufacture; **Not applicable**
- n) The inactive ingredients when a safety factor or reference to enclosed circular containing appropriate information. **Conforms.** However, the excipients should be listed in alphabetical order as per USPC official 12/1/09-5/1/10, USP 32/NF27, <1091>.
- o) The adjuvant, if present; **Not applicable**
- p) The source of the product when a factor in safe administration; **Conforms.**
- q) The identity of each microorganism used in manufacture, and where applicable, the production medium and the method of

inactivation, or reference to an enclosed circular containing appropriate information; **Not applicable**

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; **Conforms**

s) The statement “Rx only” for prescription biologicals; **Conforms**

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*]

a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label. **Not applicable.** Exempt biologic

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name. **Not applicable.** Exempt biologic

c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision. **Not applicable.** Exempt biologic

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; **Not applicable**

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. **Not applicable**

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; **Conforms**

- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] **Conforms**
- G. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**
- H. 21 CFR 201.6 Drugs; misleading statements; **Conforms**
- I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence]; **Conforms**
- J. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**
- K. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**
- L. 21 CFR 201.25 Bar code label requirements; **Conforms**
- M. 21 CFR 201.50 Statement of identity; **Conforms**
- N. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms**
- O. 21 CFR 201.55 Statement of dosage; **Conforms**
- P. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

The carton and container labels for Entyvio (vedolizumab) were found not to comply with one or more of the following regulations: 21 CFR 610.60 and 21 CFR 610.61; and United States Pharmacopeia, 5/1/13-12/31/13, USP 36/NF 31. The deficiencies identified in the carton and container labels are listed below and were communicated to the sponsor in an information request on 11/05/13. The sponsor provided the responses on 11/11/13 under sequence 125476/0.36.

Information Request:

- I. Carton and Container
 - a. Revise [REDACTED] ^{(b) (4)} to “Manufactured by:” on all labels to comply with the definition of a manufacturer [21 CFR 600.3(t), 21 CFR 610.60 and 21 CFR 610.61.]

Reviewer’s Comment: *The sponsor revised the labels as requested.*

The sponsor’s response is acceptable

- b. Please revise inactive ingredients to alphabetical order per the United States Pharmacopeia, USP 32/NF 27 (5/1/09-8/1/09)- General chapter, Labeling of Inactive Ingredients <1091>.

Reviewer's Comment: *The sponsor revised label as per USP<1091>.*

- II. CDER is working to standardize the presentation of biological to include the dosage form and route of administration with the primary presentation of the trade name and proper name. Consider the following presentation*

Reviewer's Comment: *The sponsor revised label with the FDA recommended presentation.*

The sponsor's response is acceptable

- III. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Reviewer's Comment: *The sponsor provided picture of labeled container that shows the visual area of inspection is located per 21 CFR 610.60.*

The sponsor's response is acceptable

- IV. Vial Cap and (b) (4)

- a. Please comment on if there is any text on the (b) (4) and cap (b) (4). A revised USP standard will go into effect on December 1, 2013. We refer you to the following address:

http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

Reviewer's Comment: *The sponsor confirmed that there is no text on the top surface of (b) (4) and cap (b) (4).
The sponsor response is acceptable*

*Recommended Format

Entyvio

vedolizumab

For Injection

Conclusion: The revised container and carton labels as submitted by the sponsor on 11/11/13 (STN125476.0036) are acceptable.

Revised Carton and Vial Label are copied below (copied from the submission STN125476/00.36):

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/s/

RASHMI RAWAT
11/20/2013

SARAH B KENNETT
11/20/2013

KATHLEEN A CLOUSE STREBEL
11/20/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 20, 2013

To: Kevin Bugin, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm Pharm. D., Team Leader, OPDP

Subject: BLA# 125476 - ENTYVIO (vedolizumab) Lyophilized powder for injection, for intravenous infusion (Entyvio)

Reference is made to DGIEP's consult request dated July 9, 2013, requesting review of the proposed Package Insert (PI) and Medication Guide (MG) for Entyvio.

OPDP has reviewed the proposed PI entitled, "draft-labeling-text.doc" that was available in the e-room on November 8, 2013. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

Please note that comments on the proposed MG will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
11/20/2013

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

BLA	125476
Generic Name	Vedolizumab (MLN0002)
Sponsor	Millennium Pharmaceuticals, Inc: A Takeda Oncology Company
Indication	For the treatment of 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 (TNF α) antagonist.
Dosage Form	IV Solution
Drug Class	Humanized monoclonal antibody, selective immunosuppressant
Therapeutic Dosing Regimen	300 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Unknown
Submission Number and Date	SDN 001 20 Jun 2013
Review Division	DGIEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large QTc prolongation effect of MLN0002 600 mg Process B and MLN0002 600 mg Process C was detected in this study. The largest upper bounds of the 2-sided 90% CI for the mean difference between MLN0002 600 mg Process B and MLN0002 600 mg Process C and placebo were 11.7 and 10.6 ms, respectively.

In this randomized, placebo-controlled, double-blind, parallel-group study of a single dose of i.v. 600 mg MLN0002, 87 healthy subjects received a single i.v. dose of 600 mg Process B MLN0002, a single i.v. dose of 600 mg Process C MLN0002 and a single i.v. dose of placebo. An overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MLN0002 600 mg (Process B and Process C) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Day	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
MLN0002 Process B	8	5.7	(-0.3, 11.7)
MLN0002 Process C	8	4.7	(-1.1, 10.6)

* Multiple endpoint adjustment was not applied.

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

2 BACKGROUND

2.1 PRODUCT INFORMATION

MLN0002 is a humanized IgG1 monoclonal antibody (mAb) directed against the human lymphocyte integrin, $\alpha_4\beta_7$.

2.2 MARKET APPROVAL STATUS

Vedolizumab is not approved for marketing in any country.

2.3 PRECLINICAL INFORMATION

In a single-dose CV safety pharmacology study in telemetered cynomolgus monkeys, MLN0002 (10 and 100 mg/kg) was administered to via an i.v. infusion. There were no revealed effects on electrocardiograms ECGs (both qualitative and quantitative), heart rate, or mean arterial pressure.

2.4 PREVIOUS CLINICAL EXPERIENCE

From ISS

This Integrated Summary of Safety (ISS) reviews safety data from the clinical development program for vedolizumab as treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD). The ISS presents an analysis of safety experience in 3326 subjects (1279 patients with UC, 1850 patients with CD, and 197 healthy subjects) who received at least 1 dose of vedolizumab, of whom 903 patients with either UC or CD received ≥ 24 infusions with 4 weeks of follow-up, and 415 received ≥ 36 infusions with 4 weeks of follow-up.

Reviewer's comments: there were reports of QT prolongation and one report of ventricular tachycardia. None of them were related to study drug.

2.5 CLINICAL PHARMACOLOGY

Appendix 5.1 summarizes the key features of MLN0002's clinical pharmacology.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 9125. The sponsor submitted the study report C13009 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

3.2 TQT STUDY

3.2.1 Title

A Phase 1 Single Dose Study to Determine the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of a Lyophilized Formulation (Process C Drug Product) of MLN0002 in Healthy Subjects

3.2.2 Protocol Number

C13009

3.2.3 Study Dates

24 November 2008 -- 30 November 2009

3.2.4 Objectives

- To determine the pharmacokinetics (PK) and pharmacodynamics (PD) of a single intravenous (IV) 300 mg dose of the Process C drug product of MLN0002
- To determine the PK and PD of a single IV 600 mg dose of the Process C drug product of MLN0002 relative to the Process B drug product of MLN0002
- To assess the safety and tolerability of a single IV dose of the Process C drug product of MLN0002
- To evaluate the effect of MLN0002 on cardiac repolarization

3.2.5 Study Description

3.2.5.1 Design

Part 1: open-label single dose administration of 300 mg MLN0002 Process C drug product.

Part 2: randomized, placebo controlled, double-blind, parallel-group single dose administration of 600 mg MLN0002 Process B drug product, 600 mg MLN0002 Process C drug product, or placebo.

3.2.5.2 Controls

The Sponsor used placebo but no positive (moxifloxacin) controls.

3.2.5.3 Blinding

Part 1 is not blinded. Part 2 treatment and placebo are double-blinded.

3.2.6 Treatment Regimen

3.2.6.1 Treatment Arms

Part 1

In Part 1, subjects received 300 mg Process C MLN0002 by IV administration on Day 1. Following reconstitution, 5 mL of MLN0002, obtained by pooling from 2 vials, was diluted in 0.9% sodium chloride to a final volume of 250 mL.

Part 2

Subjects in Part 2 (blinded cohort) received 600-mg MLN0002 (Process B or Process C) or the equivalent volume of placebo by IV administration on Day 1 as follows:

- For Process B, 120 mL of MLN0002, obtained by pooling 24 injection vials, was diluted in 0.9% sodium chloride to a final volume of 250 mL.
- For Process C, following reconstitution, 10 mL of MLN0002 was to be drawn by pooling from 4 vials and diluted in 0.9% sodium chloride to a final volume of 250 mL.
- For placebo, the infusion was 250 mL of sodium chloride solution, 0.9%.

3.2.6.2 Sponsor's Justification for Doses

The dose of MLN0002 selected for Part 1, 300 mg, was selected on the basis of the dose range studied during phases 1 and 2, and is the dose selected for the pivotal phase 3 studies and for product registration.

The dose of MLN0002 selected for Part 2, 600 mg, was selected on the basis of the dose range studied during phases 1 and 2, and provided similar maximum MLN0002 concentrations as the predicted maximum MLN0002 concentration at steady state for the dose regimens in the pivotal phase 3 studies and for product registration. (Page 37 in CSR)

Reviewer's Comment: Extrinsic and intrinsic factors may have effect on PK of MLN0002, resulting in a higher exposure than the level observed in this study (C13009). The potential effect of organ impairment and drug-drug interactions on the PK of MLN0002 will be explored as part of the population pharmacokinetic analysis of Phase 3 data.

3.2.6.3 Instructions with Regard to Meals

Dose was administered without regard to food.

Reviewer's Comment: Food is not expected to have an effect on PK as MLN0002 will be administered via i.v. infusion.

3.2.6.4 ECG and PK Assessments

PK samples were collected on day 1 (prior to the start of study drug infusion, 5 minutes after the end of infusion, and 1, 2, and 12 hours after the start of infusion), and Days 2 (\pm 2 days), 8 (\pm 2 days), 29 (\pm 2 days), 57 (\pm 2 days), 85 (\pm 2 days), 113 (\pm 2 days), 141 (\pm 2 days), 169 (\pm 2 days), and 197 (\pm 2 days).

ECG data were collected before (prior to the start of study drug infusion on Day 1 of both parts) and after (on Days 2 and 197 of Part 1, and Days 1, 2, 8, 29, 85, and 197 of Part 2) the administration of MLN0002. Post-dose ECGs were time matched to the pre-dose ECG to minimize any influence of diurnal variation on the QT interval. Post dose ECGs were collected during times of highest MLN0002 concentration as well as during washout (through Day 85 post administration) to fully characterize any potential acute or delayed effects of MLN0002 on cardiac repolarization.

Reviewer's Comment: The timing of PK sampling and ECGs is acceptable.

3.2.6.5 Baseline

ECG measures on Day 1 before dosing were used as baseline.

3.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

3.2.8 Sponsor's Results

3.2.8.1 Study Subjects

A total of 87 subjects were enrolled in the study. All 87 subjects were included in the safety population, and 56 subjects (10, 22, and 24 subjects in the 300-mg Process C MLN0002, 600-mg Process B MLN0002, and 600-mg Process C treatment groups MLN0002, respectively) were included in the PK and PD analysis populations. Seventy-three subjects were included in the primary ECG population and 71 subjects were included in the secondary ECG population. A total of 66 (76%) subjects completed the study; 8 (9%) subjects withdrew their consent and 13 (15%) subjects were lost to follow-up.

Table 2-Subject Disposition

N (%)	Placebo N=25	300 mg MLN0002 (Process C) N=13	600 mg MLN0002 (Process B) N=23	600 mg MLN0002 (Process C) N=26	Total N=87
Subjects Randomized	25	0	23	26	74
Safety Analysis Set ^a	25 (100)	13 (100)	23 (100)	26 (100)	87 (100)
PK Analysis Set ^b	0	10 (77)	22 (96)	24 (92)	56 (64)
PD Analysis Set ^c	0	10 (77)	22 (96)	24 (92)	56 (64)
Subjects Completing Study	20 (80)	10 (77)	19 (83)	17 (65)	66 (76)
Subjects not Completing Study, Primary Reason	5 (20)	3 (23)	4 (17)	9 (35)	21 (24)
Adverse Event	0	0	0	0	0
Protocol Violation(s)	0	0	0	0	0
Study Terminated By Sponsor	0	0	0	0	0
Withdrawal By Subject	2 (8)	1 (8)	2 (9)	3 (12)	8 (9)
Lost To Follow-Up	3 (12)	2 (15)	2 (9)	6 (23)	13 (15)
Other	0	0	0	0	0

Source: CSR, Table 14.1.1.1.

3.2.8.2 Statistical Analyses

3.2.8.2.1 Primary Analysis

The safety population, defined as all subjects receiving any amount of study drug, was used to evaluate the safety and tolerability (including clinical safety and immunogenicity) of MLN0002. The population for PK and PD analyses included all subjects in Part 1 and Part 2 who received the dose of active drug and had sufficient blood sampling to allow for PK and PD evaluation (as determined by the responsible pharmacologist), but excluded subjects with positive HAHA at any time point after study drug administration. There were 2 ECG populations defined for the clinical study report. The primary ECG population was defined as the safety population. The secondary ECG population was defined as the primary ECG population but with the exclusion of subjects who did not have PK profiles that were consistent with IV administration.

For the primary ECG population, changes from baseline in QTcF by study visit are presented in Table 12-5. The largest time matched mean baseline adjusted difference of the MLN0002 and placebo was observed at Day 8. The mean change from baseline was -4.5 for placebo and 0.6 for MLN0002. The 1- sided 95% (or 2-sided 90%) upper confidence bound for the largest mean change adjusted for placebo was 9.3 observed on Day 8. The upper bound of 95% 1-sided confidence interval for the largest time-matched mean effect of MLN0002 on the QTc interval excluded 10 msec, which is the threshold for pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation (based on the E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs). Overall, no effect of MLN0002 on QTc was observed.

For the secondary ECG population, Changes from baseline in QTcF by study visit are presented in Table 12-6. The largest mean baseline adjusted difference of MLN0002 and placebo was observed at Day 8. The 1- sided 95% (or 2-sided 90%) upper confidence bound of 8.1 was observed for the secondary ECG population.

ECG results for the secondary ECG population were similar to those of the primary ECG population.

3.2.8.2.2 Categorical Analysis

Overall, there were no marked mean changes in ECG parameters. Two (8%) subjects in the placebo treatment group and 10 (20%) subjects in the MLN0002 treatment group had maximum post baseline QTcF values of between 430 to 449 msec, and 7 (14%) subjects in the MLN0002 treatment group had maximum post baseline QTcB values between 430 to 449 msec (Tables 14.4.4.5D, 14.4.4.5E, and 14.4.4.5F). Four (17%) subjects in the placebo treatment group and 4 (9%) subjects in the MLN0002 treatment group had a ≥ 30 msec change in QTcB, and 2 (4%) subjects in the MLN0002 treatment group had a ≥ 30 msec change in QTcF (Tables 14.4.4.5D, 14.4.4.5E, and 14.4.4.5F). No subjects had QTc > 450 msec or had ≥ 60 msec change in QTc from baseline.

One (5%) subject (58300-249) in the placebo treatment group had an ECG abnormality on Day 85 that was considered to be clinically significant (Table 14.4.4.5K). The abnormality was reported as a single, mild, drug-related cardiac AE of atrial fibrillation; no action was taken and the event resolved (Tables 14.4.1.2 and 14.4.1.5, Listing 16.2.7.1).

Though some subjects in the MLN0002 treatment groups had abnormal ECG parameters during the study, none were considered clinically significant (Table 14.4.4.5K).

3.2.8.3 Safety Analysis

There were no on-study deaths in the study. Overall, 1 subject (58300-249) in the placebo treatment group experienced 1 mild treatment-emergent cardiac event AE, atrial fibrillation; no action was taken and the event resolved.

3.2.8.4 Clinical Pharmacology

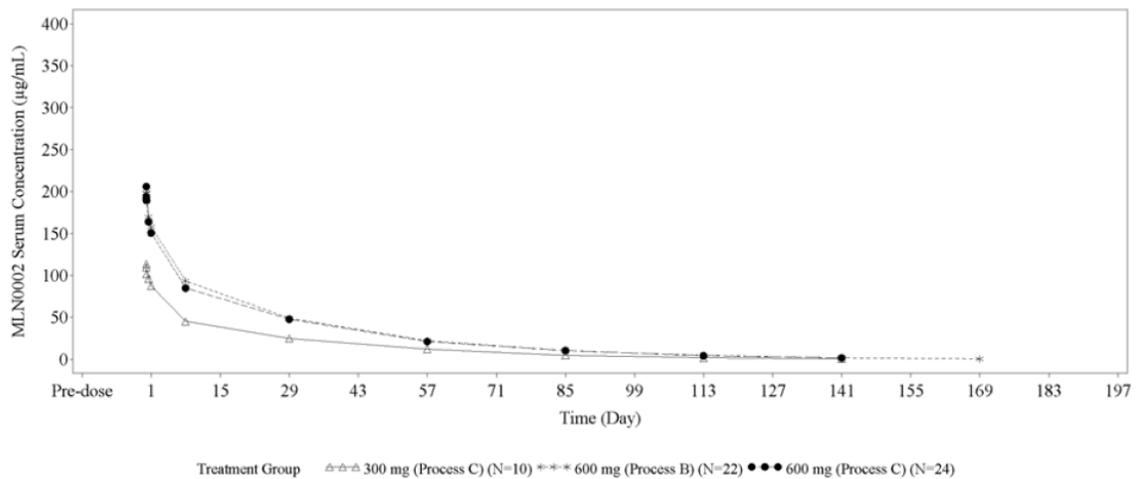
3.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3 and Figure 1. The mean time-course concentration curve for 600 mg process B and process C are very similar. The AUC and C_{\max} of 600 mg are twice as high as 300 mg.

Table 3: PK Parameters of MLN0002 by Treatment Group

Parameter	Units	Treatment Group	n	Geometric Mean	Arithmetic Mean	CV%
C _{max}	µg/mL	300 mg Process C	10	115	120	31.1
		600 mg Process C	24	206	211	23.7
		600 mg Process B	21	205	207	12.6
AUC _{0-inf}	µg*d/mL	300 mg Process C	8	2000	2020	13.2
		600 mg Process C	22	3890	3970	20.7
		600 mg Process B	19	4040	4080	16.1
AUC _{0-last}	µg*d/mL	300 mg Process C	8	1990	2000	13.5
		600 mg Process C	22	3750	3840	22.9
		600 mg Process B	19	3980	4030	17.1

Figure 1: PK Profile of MLN0002 by Treatment Group



3.2.8.4.2 Exposure-Response Analysis

Sponsor did not perform exposure-response for QT prolongation.

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ vs. MLN0002 concentrations is presented in Figure 4. No evident E-R relationship was identified.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

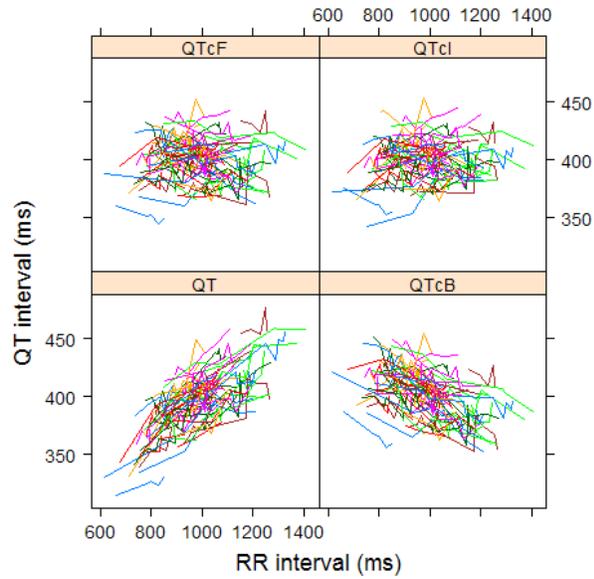
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 4, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

method	Treatment							
	600 mg (Process B)		600 mg (Process C)		Placebo		All	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	23	0.0106	26	0.0137	24	0.0122	73	0.0122
QTcF	23	0.0027	26	0.0114	24	0.0052	73	0.0066

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



4.2 STATISTICAL ASSESSMENTS

4.2.1 QTc Analysis

4.2.1.1 The Primary Analysis for MLN0002

The statistical reviewer used linear regression model to analyze the Δ QTcF effect. The model includes treatment, gender. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = MLN0002 Process B and MLN0002 Process C

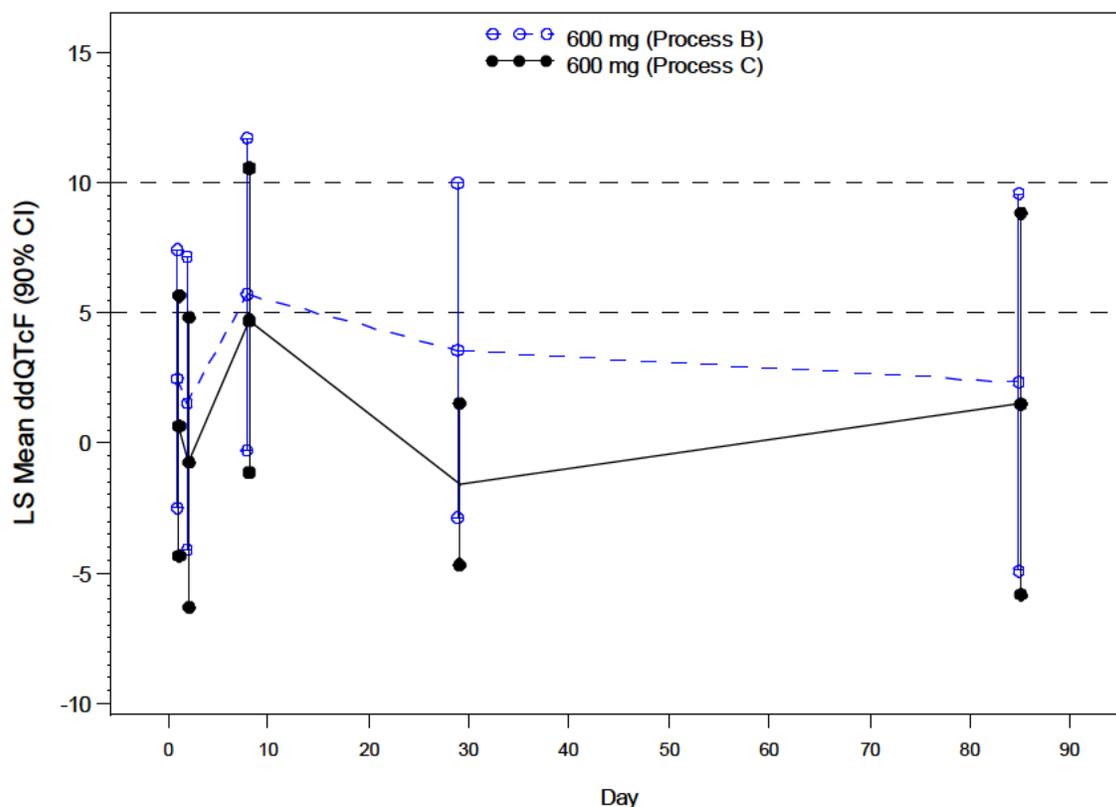
Day	Placebo dQTcF	600 mg (Process B) dQTcF	ddQTcF		600 mg (Process C) dQTcF	ddQTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-0.7	1.8	2.5	(-2.5, 7.4)	-0.0	0.6	(-4.3, 5.6)
2	-3.7	-2.1	1.5	(-4.1, 7.2)	-4.4	-0.7	(-6.3, 4.8)
8	-4.5	1.2	5.7	(-0.3, 11.7)	0.2	4.7	(-1.1, 10.6)
29	0.9	4.4	3.6	(-2.9, 10.0)	-3.8	-4.7	(-10.9, 1.5)
85	-1.6	0.8	2.3	(-4.9, 9.6)	-0.1	1.5	(-5.8, 8.8)

The largest upper bounds of the 2-sided 90% CI for the mean difference between MLN0002 Process B and placebo, and between MLN0002 Process C and placebo were 11.7 ms and 10.6 ms, respectively.

4.2.1.2 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



4.2.1.3 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, and greater than 450 ms. No subject's QTcF was above 450 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N		Value ≤ 450 ms		Value > 450 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
600 mg (Process B)	23	101	23 (100%)	101 (100%)	0 (.%)	0 (0.0%)
600 mg (Process C)	26	121	26 (100%)	121 (100%)	0 (.%)	0 (0.0%)
Placebo	24	115	24 (100%)	115 (100%)	0 (.%)	0 (0.0%)

Table 7 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 7: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
600 mg (Process B)	21	94	19 (90.5%)	91 (96.8%)	2 (9.5%)	3 (3.2%)	0 (.%)	0 (0.0%)
600 mg (Process C)	24	114	24 (100%)	114 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)
Placebo	24	115	24 (100%)	115 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)

4.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean difference between MLN0002 Process B and placebo, and between MLN0002 Process C and placebo were 6.9 bpm and 4.7 bpm, respectively. No subject under treatment had HR>100 bpm.

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = MLN0002 Process B and MLN0002 Process C

Day	Placebo dHR	600 mg (Process B) dHR	ddHR		600 mg (Process C) dHR	ddHR	
	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
1	0.1	1.7	1.6	(-1.2, 4.4)	0.7	0.6	(-2.1, 3.3)
2	-0.3	-1.3	-1.1	(-3.6, 1.4)	-0.8	-0.6	(-2.9, 1.8)
8	4.6	1.4	-3.1	(-8.8, 2.5)	2.0	-2.6	(-7.9, 2.7)
29	4.1	4.4	0.3	(-4.4, 4.9)	-0.4	-4.4	(-8.7, -0.1)
85	0.2	2.4	2.1	(-2.7, 6.9)	0.3	0.0	(-4.6, 4.7)

Table 9: Categorical Analysis for HR

Treatment Group	Total N		Value≤100 bpm		Value>100 bpm	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
600 mg (Process B)	23	101	23 (100%)	101 (100%)	0 (.%)	0 (0.0%)
600 mg (Process C)	26	121	26 (100%)	121 (100%)	0 (.%)	0 (0.0%)
Placebo	24	115	24 (100%)	115 (100%)	0 (.%)	0 (0.0%)

4.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the PR mean differences between MLN0002 Process B and placebo, and between MLN0002 Process C and placebo were 11.1 ms and 7.6 ms, respectively.

The outlier analysis results for PR are presented in Table 11.

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = MLN0002 Process B and MLN0002 Process C

Day	Placebo dPR	600 mg (Process B) dPR	ddPR		600 mg (Process C) dPR	ddPR	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-0.3	-1.1	-0.8	(-5.4, 3.8)	-2.3	-2.0	(-6.5, 2.5)
2	-1.1	1.6	2.7	(-1.3, 6.7)	1.8	2.9	(-0.9, 6.7)
8	0.0	3.1	3.1	(-2.5, 8.7)	1.3	1.3	(-3.9, 6.5)
29	0.8	4.9	4.1	(-2.9, 11.1)	1.9	1.1	(-5.4, 7.6)
85	2.5	0.4	-2.1	(-8.2, 3.9)	1.9	-0.6	(-6.5, 5.3)

Table 11: Categorical Analysis for PR

Treatment Group	Total		Value ≤ 200 ms		Value > 200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
600 mg (Process B)	23	101	23 (100%)	101 (100%)	0 (0.0%)	0 (0.0%)
600 mg (Process C)	26	121	24 (92.3%)	115 (95.0%)	2 (7.7%)	6 (5.0%)
Placebo	24	114	22 (91.7%)	109 (95.6%)	2 (8.3%)	5 (4.4%)

4.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12.

The largest upper limits of 90% CI for the QRS mean differences between MLN0002 Process B and placebo, and between MLN0002 Process C and placebo were 6.4 ms and 5.0 ms, respectively. There is one subject who experienced QRS interval greater than 110 ms in MLN0002 Process B group.

The outlier analysis results for QRS are presented in Table 13.

Table 12: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = MLN0002 Process B and MLN0002 Process C

Day	Placebo dQRS	600 mg (Process B) dQRS	ddQRS		600 mg (Process C) dQRS	ddQRS	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	0.2	-0.5	-0.7	(-2.6, 1.3)	-1.3	-1.5	(-3.4, 0.4)
2	-0.4	0.4	0.7	(-1.5, 3.0)	0.5	0.9	(-1.3, 3.1)
8	-1.3	1.0	2.4	(-0.5, 5.2)	0.0	1.4	(-1.3, 4.0)
29	0.1	1.8	1.7	(-1.7, 5.1)	-0.2	-0.3	(-3.5, 2.8)
85	-1.5	1.9	3.5	(0.5, 6.4)	0.6	2.1	(-0.8, 5.0)

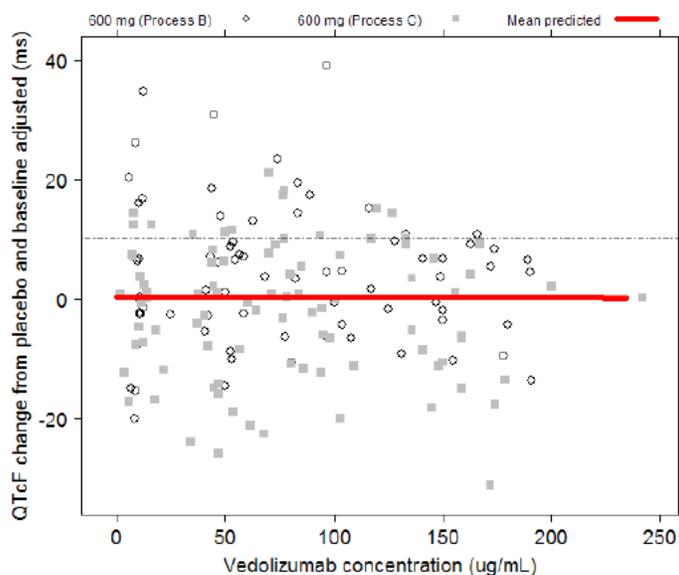
Table 13: Categorical Analysis for QRS

Treatment Group	Total		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
600 mg (Process B)	23	101	21 (91.3%)	91 (90.1%)	1 (4.3%)	9 (8.9%)	1 (4.3%)	1 (1.0%)
600 mg (Process C)	26	121	21 (80.8%)	114 (94.2%)	5 (19.2%)	7 (5.8%)	0 (0.0%)	0 (0.0%)
Placebo	24	115	19 (79.2%)	101 (87.8%)	3 (12.5%)	11 (9.6%)	2 (8.3%)	3 (2.6%)

4.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcF and MLN0002 concentrations is visualized in Figure 4 with no evident exposure-response relationship.

Figure 4: $\Delta\Delta$ QTcF vs. MLN0002 concentration



4.4 CLINICAL ASSESSMENTS

4.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

4.4.2 ECG assessments

Sponsor did not upload ECGs.

4.4.3 PR and QRS Interval

Two subjects had a PR >200 ms, one at baseline. One subject had a QRS > 110 ms at baseline.

5 APPENDIX

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	300 mg MLN0002 on weeks 0, 2 and 6, then every 4 or 8 weeks thereafter.																										
Maximum tolerated dose	The maximum tolerated dose was not studied. Ten (10) mg/kg was the highest tested dose in healthy volunteers and patients and was generally well tolerated.																										
Principal adverse events	<p>Overall, the percentages of healthy subjects and patients who reported AEs, SAEs, and discontinuations due to AEs were similar between the subjects in the combined MLN0002 group (includes all healthy subjects and patients treated with any dose of MLN0002) and the subjects in the placebo group (includes all healthy subjects and patients who received placebo). Throughout the MLN0002 program, there has been no overt relationship identified between dose and specific AEs. There were no on-study deaths.</p> <p>The most commonly reported AEs in the MLN0002 group were headache (26% in the MLN0002 group vs 21% in the placebo group), nausea (15% vs 15%, respectively), ulcerative colitis (15% vs 18%, respectively), abdominal pain (12% vs 17%, respectively), fatigue (12% vs 12%, respectively), and nasopharyngitis (10% vs 7%, respectively).</p>																										
Maximum dose tested	Single Dose	10 mg/kg																									
	Multiple Dose	10 mg/kg on weeks 0, 2, 4 and 8																									
Exposures Achieved at Maximum Tested Dose	Single Dose	C _{max} : 243 mg/L (9.07 %) AUC _{0-inf} : 4880 d*mg/L (13.0 %)																									
	Multiple Dose	Dosing on weeks 0, 2, 4 and 8. Multiple Dose PK obtained after dosing on Week 8. <i>Preliminary data analysis.</i> C _{max} : 292 mg/L (32.6 %) AUC _{0-inf} : 28300 d*mg/L (35.5 %)																									
Range of linear PK	2 – 10 mg/kg																										
Accumulation at steady state	Data not available. Study analysis is ongoing.																										
Metabolites	MLN0002 is a therapeutic monoclonal antibody and therefore no metabolism experiments have been performed.																										
Absorption	Absolute/Relative Bioavailability	Not evaluated. MLN0002 is currently being investigated for administration as an intravenous infusion.																									
	T _{max}	Not evaluated. MLN0002 is currently being investigated for administration as an intravenous infusion.																									
Distribution	V _d /F or V _d	<table border="1"> <thead> <tr> <th>Dose</th> <th>Mean (L)</th> <th>SD</th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>0.2 mg/kg</td> <td>4.02</td> <td>0.151</td> <td>3.76</td> </tr> <tr> <td>0.5 mg/kg</td> <td>4.92</td> <td>0.620</td> <td>12.6</td> </tr> <tr> <td>2.0 mg/kg</td> <td>3.34</td> <td>0.665</td> <td>19.9</td> </tr> <tr> <td>6.0 mg/kg</td> <td>2.98</td> <td>0.644</td> <td>21.6</td> </tr> <tr> <td>10.0 mg/kg</td> <td>2.89</td> <td>1.02</td> <td>35.2</td> </tr> </tbody> </table>		Dose	Mean (L)	SD	CV%	0.2 mg/kg	4.02	0.151	3.76	0.5 mg/kg	4.92	0.620	12.6	2.0 mg/kg	3.34	0.665	19.9	6.0 mg/kg	2.98	0.644	21.6	10.0 mg/kg	2.89	1.02	35.2
	Dose	Mean (L)	SD	CV%																							
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0.5 mg/kg	4.92	0.620	12.6																								
2.0 mg/kg	3.34	0.665	19.9																								
6.0 mg/kg	2.98	0.644	21.6																								
10.0 mg/kg	2.89	1.02	35.2																								
	% bound	Not evaluated.																									

Elimination	Route	MLN0002 is a therapeutic monoclonal antibody and therefore, no dedicated elimination experiments have been performed. Subsequent to administration, the primary route of elimination is likely to be proteolytic degradation similar to that of physiological immunoglobulins. The resultant amino acids are recycled and available for incorporation into endogenous proteins.																								
	Terminal t _{1/2}	<table border="1"> <thead> <tr> <th>Dose</th> <th>Mean (day)</th> <th>SD</th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>0.2 mg/kg</td> <td>6.79</td> <td>0.736</td> <td>10.8</td> </tr> <tr> <td>0.5 mg/kg</td> <td>11.7</td> <td>2.83</td> <td>24.2</td> </tr> <tr> <td>2.0 mg/kg</td> <td>14.1</td> <td>2.67</td> <td>18.9</td> </tr> <tr> <td>6.0 mg/kg</td> <td>15.1</td> <td>3.15</td> <td>20.9</td> </tr> <tr> <td>10.0 mg/kg</td> <td>14.8</td> <td>7.38</td> <td>49.8</td> </tr> </tbody> </table>	Dose	Mean (day)	SD	CV%	0.2 mg/kg	6.79	0.736	10.8	0.5 mg/kg	11.7	2.83	24.2	2.0 mg/kg	14.1	2.67	18.9	6.0 mg/kg	15.1	3.15	20.9	10.0 mg/kg	14.8	7.38	49.8
	Dose	Mean (day)	SD	CV%																						
0.2 mg/kg	6.79	0.736	10.8																							
0.5 mg/kg	11.7	2.83	24.2																							
2.0 mg/kg	14.1	2.67	18.9																							
6.0 mg/kg	15.1	3.15	20.9																							
10.0 mg/kg	14.8	7.38	49.8																							
CL/F or CL	<table border="1"> <thead> <tr> <th>Dose</th> <th>Mean (L/hr)</th> <th>SD</th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>0.2 mg/kg</td> <td>0.017</td> <td>0.002</td> <td>9.89</td> </tr> <tr> <td>0.5 mg/kg</td> <td>0.013</td> <td>0.004</td> <td>34.5</td> </tr> <tr> <td>2.0 mg/kg</td> <td>0.007</td> <td>0.001</td> <td>10.9</td> </tr> <tr> <td>6.0 mg/kg</td> <td>0.006</td> <td>0.001</td> <td>21.6</td> </tr> <tr> <td>10.0 mg/kg</td> <td>0.006</td> <td>0.001</td> <td>17.1</td> </tr> </tbody> </table>	Dose	Mean (L/hr)	SD	CV%	0.2 mg/kg	0.017	0.002	9.89	0.5 mg/kg	0.013	0.004	34.5	2.0 mg/kg	0.007	0.001	10.9	6.0 mg/kg	0.006	0.001	21.6	10.0 mg/kg	0.006	0.001	17.1	
Dose	Mean (L/hr)	SD	CV%																							
0.2 mg/kg	0.017	0.002	9.89																							
0.5 mg/kg	0.013	0.004	34.5																							
2.0 mg/kg	0.007	0.001	10.9																							
6.0 mg/kg	0.006	0.001	21.6																							
10.0 mg/kg	0.006	0.001	17.1																							
Intrinsic Factors	Age	The current PK data do not suggest an age effect. The impact of age on the disposition of MLN0002 will be assessed within the phase 3 population pharmacokinetic analysis.																								
	Sex	The current PK data do not suggest a gender difference. The impact of sex on the disposition of MLN0002 will be assessed within the phase 3 population pharmacokinetic analysis.																								
	Race	The current PK data do not suggest a race difference. The impact of race on the disposition of MLN0002 will be assessed within the phase 3 population pharmacokinetic analysis.																								
	Hepatic & Renal Impairment	Dedicated PK studies are not planned to be performed for this population. Depending on the patient characteristics of the Phase 3 programs, the impact of renal and hepatic function on the disposition of MLN0002 will be assessed within the phase 3 population pharmacokinetic analysis.																								
Extrinsic Factors	Drug interactions	No dedicated DDI studies have been performed for MLN0002. Drug-drug interactions will be assessed within the phase 3 population pharmacokinetic analysis. Depending on the impact of identified DDIs, dedicated DDI studies would be considered.																								
	Food Effects	Not evaluated. MLN0002 is currently being investigated for administration as an intravenous infusion.																								
Expected High Clinical Exposure Scenario	The current clinical data set has evaluated the safety and tolerability of doses up to 10 mg/kg. In both patients and healthy volunteers, this dose was generally well tolerated. The proposed dose for phase 3 (and ultimately for registration) is 300 mg, which is approximately 4 mg/kg. Therefore, the current clinical data set covers a margin of up to a 2.5-fold increase in exposure and suggests no critical safety issue.																									

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QIANYU DANG
09/27/2013

JINGYU YU
09/27/2013

KEVIN M KRUDYS
10/01/2013

MONICA L FISZMAN
10/01/2013

NORMAN L STOCKBRIDGE
10/01/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: [BLA 125476&BLA 125507](#)

Application Type: [New BLAs](#)

Name of Drug: Entyvio (vedolizumab) 300 mg, IV

Applicant: Takeda Pharmaceuticals USA, Inc

Submission Date: 06/20/2013

Receipt Date: 06/20/2013

1.0 Regulatory History and Applicant's Main Proposals

This biologics license application (BLA) is submitted in support of marketing approval of vedolizumab for injection for the treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's Disease (CD). UC and CD are serious chronic lifelong diseases that cause considerable morbidity in a relatively young patient population, and, despite existing pharmacological treatments, significant unmet medical need remains.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 13, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

NO

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *Applicant includes the Use in Specific Populations sections yet the section does not appear to include actionable information.*

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

Selected Requirements of Prescribing Information (SRPI)

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

NO

Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment: Applicant should revise such that only the name of class is used, i.e. "integrin antagonist."

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

Selected Requirements of Prescribing Information (SRPI)

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS

Selected Requirements of Prescribing Information (SRPI)

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

PI provides (b) (4) rather than “see FDA-approved patient labeling (Medication Guide)”.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN B BUGIN
08/30/2013

RICHARD W ISHIHARA
08/30/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125476&125507	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Entyvio (see IND 009125) Established/Proper Name: vedolizumab Dosage Form: injectable Strengths: 300 mg		
Applicant: Takeda Pharmaceuticals USA Inc Agent for Applicant (if applicable): Millennium Pharmaceuticals, Inc		
Date of Application: 06/20/2013 Date of Receipt: 06/20/2013 Date clock started after UN:		
PDUFA Goal Date: 02/18/2014 (B125476); 06/18/2014(B125507)	Action Goal Date (if different): 02/14/2014 (B 125476)	
Filing Date: 08/19/2013	Date of Filing Meeting: 07/22/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): BLA 125476 (moderate to severe ulcerative colitis) & BLA 125507 (moderate to severe Crohn's disease)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard BLA 125507 (CD) <input checked="" type="checkbox"/> Priority BLA 125476 (UC) <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			X																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			X																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i></p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															X	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		X																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA</i> s/ <i>NDA</i> efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?			X	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			PeRC scheduled for Nov 06
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Combination Waiver/Deferral Request
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Was submitted to IND 009125, and is tentatively approved.
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			Consult to DRISK sent and OSI RMP invited to all milestone meetings.
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Lisa Kholsa is reviewing from DMEPA and Kim Rains is reviewing from OBP.
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			QT-IRT; CDRH-OIVD
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 04/18/2008; 06/05/2008; 09/26/2008;	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11/06/2012; 11/13/2012;	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 07/22/2013

BLA/NDA/Supp #: 125476 & 125507

PROPRIETARY NAME: Entyvio

ESTABLISHED/PROPER NAME: vedolizumab

DOSAGE FORM/STRENGTH: I.V., 300 mg

APPLICANT: Millennium Pharmaceuticals, Inc: A Takeda Oncology Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

For the treatment of 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 (TNF α) antagonist.

- And -

For the treatment of 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 (TNF α) antagonist.

BACKGROUND:

This biologics license application (BLA) is submitted in support of marketing approval of vedolizumab for injection for the treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's Disease (CD). UC and CD are serious chronic lifelong diseases that cause considerable morbidity in a relatively young patient population, and, despite existing pharmacological treatments, significant unmet medical need remains.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kevin Bugin	Y
	CPMS/TL:	Richard Ishihara	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y

Clinical	Reviewer:	Laurie Muldowney; Klaus Gottlieb	Y
	TL:	Anil Rajpal	Y

Clinical Pharmacology	Reviewer:	Lanyan (Lucy) Fang	Y
	TL:	Yow-Ming Wang	Y
Biostatistics	Reviewer:	Milton Fan	Y
	TL:	Steve Wilson/Mike Welch	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti	Y
	TL:	Sushanta Chakder	Y
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Qing (Joanna) Zhou	Y
	TL:	Rashmi Rawat	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steve Fong; Reyes Candauchacon	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Kim Rains	Y
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:	Peter Qiu	Y
OSE/DMEPA (proprietary name)	Reviewer:	Lisa Khosla	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:	Kendra Worthy	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:	Susan Leibenhaut	Y
Other reviewers	Clara Kim; John Yap; Nitin Mehrotra; Justin Earp; Phong (Pete) Do;		Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: No comments.</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date if known: 12/09/2013 <input type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments: DMA	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: DMA	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Julie Beitz</p>	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 09/26/2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): See attached.

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review for Crohn’s disease (BLA 125507)</p> <p><input checked="" type="checkbox"/> Priority Review for ulcerative colitis (BLA 125476)</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN B BUGIN
08/30/2013

RICHARD W ISHIHARA
08/30/2013