CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125476Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125507 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DGIEP PDUFA Goal Date: 06/20/2014 Stamp Date: 6/20/2013

Proprietary Name: Entyvio

Established/Generic Name: Vedolizumab

Dosage Form: IV Infusion

Applicant/Sponsor: Takeda

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) none
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: "...for reducing signs and symptoms, inducing and maintaining clinical response and remission, and achieving corticosteroid-free remission in adult patients with moderately to severly active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha antagonist."

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

- ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☒ Deferred for some or all pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☒	Neonate	0 wk. __ mo.	__ wk. 1 mo.	☒	☐	☐	☐
☒	Other	__ yr. 1 mo.	5 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

☒ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☒ Too few children with disease/condition to study

☒ Other (e.g., patients geographically dispersed): Approximately 100,000 children under the age of 18 have inflammatory bowel diseases, which include Crohn's disease (CD) and ulcerative colitis (UC). However, in a study, 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 under 6 years of age. Therefore, a waiver, excluding subjects under the age of 6, from enrollment in future pediatric CD studies with vedolizumab should be granted.

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∧ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☒	☐	☐	☐
☒	Other	6 yr. __ mo.	16 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): September 2022						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

diatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

ditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other diatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the oduct are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

ıication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below).

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

	Population	minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

ction F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
]	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

evised: 6/2008)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125476	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: ENTYVIO Established/Proper Name: vedolizumab Dosage Form: for injection, for intravenous use		Applicant: Takeda Pharmaceuticals America, Inc Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: DGIEP

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 05/20/2104	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates 04/29/2014;
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☒ Other NEJM Artcile
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 05/20/2014
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included See PI
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	08/20/2013 08/20/2013
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 08/30/2013 DMEPA: ☐ None 11/26/2013 DMPP/PLT (DRISK): ☐ None 11/25/2013 OPDP: ☐ None 11/20/2013 SEALD: ☐ None CSS: ☒ None Other: ☐ None DMA 11/20/2013; OSE/OPE 08/20/2013;
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	08/30/2013 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 01/08/2014 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	04/29/2014; 04/25/2014; 04/25/2014; 04/21/2014; 04/17/2014; 04/15/2014; 04/11/2014; 04/10/2014; 04/10/2014; 04/03/2014; 04/01/2014; 04/01/2014; 03/21/2014; 03/05/2014; 02/28/2014; 02/28/2014; 02/19/2014; 02/07/2014; 02/07/2014; 02/03/2014; 01/23/2014; 01/17/2014; 01/17/2014; 01/14/2014; 01/13/2014; 01/06/2014; 12/23/2013; 12/04/2013; 12/03/2013; 12/03/2013; 11/21/2013; 11/19/2013; 11/15/2013; 11/15/2013; 11/15/2013; 11/14/2013; 11/13/2013; 11/08/2013; 11/08/2013; 11/05/2013; 10/30/2013; 10/30/2013; 10/25/2013; 10/23/2013; 10/16/2013; 10/16/2013; 10/09/2013; 10/07/2013; 09/26/2013; 09/23/2013; 09/20/2013; 09/19/2013; 09/19/2013; 09/16/2013; 09/03/2013; 08/30/2013; 08/23/2013; 08/19/2013; 08/19/2013; 08/08/2013l; 08/02/2013; 07/31/2013; 07/23/2013; 07/22/2013; 06/27/2013; 06/27/2013; 06/12/2013; 06/05/2013;
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11/06/2012; 11/13/2012;
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 09/26/2008;
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 10/04/2013;
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 11/26/2013;

• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	07/25/2012; 07/24/2012;
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	12/09/2013; 07/20/2011;
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 05/20/2014
Division Director Summary Review *(indicate date for each review)*	☐ None 05/20/2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 05/20/2014
PMR/PMC Development Templates *(indicate total number)*	☐ None 23
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	04/11/2014; 12/30/2013; 11/20/2013; 08/19/2013; 08/09/2013;
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Reviews dated 11/20/2013 and 12/30/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None 01/29/2014; 01/24/2014; 12/20/2013; 10/01/2013;
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 02/10/2014; 01/28/2014; 01/28/2014; 01/02/2014;
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 05/19/2014
Statistical Review(s) *(indicate date for each review)*	☐ None 05/19/2014; 05/15/201411/22/2013; 11/20/2013; 08/13/2013;

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 04/04/2014; 11/08/2013; 07/25/2013;
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 11/26/2013;
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 04/11/2014; 11/20/2013; 07/16/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None 11/21/2014 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ No separate review 11/27/2013;
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 02/20/2014; 11/20/2013; 08/09/2013;
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 04/16/2014; 04/14/2014; 12/12/2013; 11/26/2013; 07/09/2013;
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/20/2013;
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: 05/02/2014 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

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/s/

KEVIN B BUGIN
05/20/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Pending Information Request - Clinical (Safety) - May 01, 2014
Date:	Thursday, May 01, 2014 12:17:32 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing your response to our prior requests for information related to the postmarketing observational study and have the following request for more information. We request you provide your response by May 09, 2014, COB.

> Please provide revised power calculations that provides the sample sizes that would be needed to detect a minimum detectable incidence rate ratio (IRR) (or hazard ratio) for a range of IRRs (1.1, 1.2, 1.5, 1.75, 2.0, 2.5 and 3.0) and range of powers (80%, 90%, 95%) for an assumed average rate in the comparator group of UC and CD patients. For the background rate in the comparator group, please provide an average estimate that takes into account the rate of serious infections for both the UC and CD populations, instead of just the CD population. Please justify the proposed background rates across both disease populations as well as how the average background rate was calculated across both disease populations.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
05/01/2014

From: Bugin, Kevin
To: Quinn, Karen (Karen.Quinn@takeda.com)
Cc: Costello, Colleen (Colleen.Costello@takeda.com); Bugin, Kevin
Subject: BLA 125476 ENTYVIO (vedolizumab) - PMC Discussion Comments (CMC) - April 29, 2014
Date: Tuesday, April 29, 2014 9:55:24 AM

Hi Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

The following represents the final text of the CMC Post-Marketing Commitments to be associated with your product vedolizumab. Please confirm your agreement with the text and milestone dates as written below. We request you respond by May 06, 2014, COB.

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

    Final Study Report: December 31, 2014

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

    Final Study Report: September 30, 2014

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

    Final Study Report: December 31, 2014

4. To develop a non-reducing SDS-based assay that is capable of providing quantitative data for the evaluation of size-related impurities and to implement this assay in the release and stability programs for vedolizumab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

    Final Study Report: February 29, 2016

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

    Final Study Report: December 31, 2014

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

Final Study Report: December 31, 2014

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

Final Study Report: December 31, 2017

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

Final Study Report: December 31, 2016

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

Final Study Report: December 31, 2018

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/29/2014

From: Bugin, Kevin
To: Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Quinn, Karen (Karen.Quinn@takeda.com); Bugin, Kevin
Subject: BLA ENTYVIO (vedolizumab) - Post-Marketing Requirement/Commitment Comments - April 25, 2014
Date: Friday, April 25, 2014 8:45:38 AM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We have reviewed your April 14, 2014 response to our PMR/PMC comments communicated on April 10, 2014. We have the following comments to convey.

- The requirement to conduct a juvenile animal toxicology study for this application was requested by the Division under the Pediatric Research Equity Act (PREA) and supported by the Pediatric Research Committee (PeRC) as a necessary component of the pediatric drug development program for your product. We considered that in the PPND study, adequate exposure and target saturation were not achieved in infants on postpartum rats beyond 28 days. And 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. In addition, the age of the monkeys used in 13-week and 26-week toxicology studies do not support the proposed pediatric age group of (b) (4) years. (b) (4) .

- Similarly, the requirement of the PK/PD, safety and tolerability study in patients 5 – 17 years of age to be "dose-ranging" was required under PREA and supported by the PeRC, (b) (4)

- We have reviewed your rationale for the proposed milestone dates for the pediatric PMRs. We accept the proposed dates for trial completion and report submission, but we request the originally proposed dates for the final protocol submission dates. The final PREA PMRs and milestone dates will reflect the above.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/25/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Quinn, Karen (Karen.Quinn@takeda.com); Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Enhanced Pharmacovigilance Plan Advice - April 24, 2014
Date:	Friday, April 25, 2014 8:02:19 AM
Attachments:	HEPATIC SIAE GLOBAL FOLLOW-UP FORM.PDF

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Below please find recommendations regarding the enhanced pharmacovigilance plan. In addition, comments on your hepatic follow-up form is attached. We request you respond by May 02, 2014.

1 RECOMMENDATIONS

In addition to the applicant's proposal for an enhanced pharmacovigilance (EPV) plan for infections, PML, and liver Injury, FDA requests an additional EPV plan for tumor and malignancies. See below for specific recommendations for each safety risk.

1.1 Expedited 15-day Reporting

1.1.1 Infections

In addition to the Applicant's proposal for EPV plan of infections, FDA recommends that the Applicant provide expedited 15-day reporting of gastrointestinal and systemic infection adverse events (AEs) defined as MedDRA PTs assigned to the high-level group term (HLGT) Gastrointestinal infections and high-level term (HLT) Sepsis, bacteraemia, viraemia and fungaemia NEC for all outcomes and regardless of seriousness, report source or labeling status.

1.1.2 Neurologic Events Consistent with Possible PML

FDA requests a plan for follow up reports of neurologic symptoms consistent with possible PML to verify or exclude the diagnosis of PML. Please indicate whether a report of possible PML is *Suspect PML*, *Confirmed PML* or *PML excluded*. Please provide expedited reporting of any cases of neurologic symptoms consistent with possible PML from spontaneous and literature reports, as well as from Study MLN-0002_401, regardless of seriousness, report source or labeling status.

FDA recommends changing the title from *Neurologic Events or PML* to *Neurologic Events Consistent with Possible PML* and the bi-annual assessment to only include cases suggestive of possible PML.

FDA finds the Applicant's PML Follow-up Checklist acceptable.

1.1.3 Liver Injury

FDA requests a plan for follow up of reports consistent with possible liver injury to obtain information regarding final diagnosis and adding the Liver related investigations, signs and symptoms SMQ and Liver Infections SMQ to the inclusion criteria for 15-day expedited reporting of liver injury. Please add to the submitted Hepatic SIAE Global Follow-up Form information to

capture trends of laboratory data (e.g. liver enzymes and liver function) in addition to the laboratory baseline, peak and nadir currently proposed; see attached Hepatic SIAE Global Follow-up Form with comments.

1.1.4 Tumor and Malignancies

FDA requests the addition of an EPV plan for expedited reporting of adverse events of any tumors and malignancy regardless of seriousness, report source, or labeling status.

1.2 Bi-Annual Periodic Post Market Safety Assessment

1. For all assessments, present data by reporting interval and cumulative since drug approval.
2. Safety assessment of post-market reports (spontaneous and from study MLN-0002_401and C13008) consistent with infections, PML, liver injury, or tumor and malignancy should include, but not limited to the following:
    - Indication for treatment with vedolizumab
    - Previous immunosuppressive or immunomodulating therapy with specific dates and duration of therapy
    - US vs. Rest of World (ROW)
    - Report source (e.g., spontaneous report, study, etc.)
    - Patient demographics (e.g., age, sex, etc.)
    - Concomitant therapy
    - Underlying medical conditions
    - Presenting symptoms and time to diagnosis of adverse event
    - Severity of adverse event: quantitative laboratory or objective measurements where applicable (e.g. neurologic deficit for PML, peak and trends of laboratory tests for liver toxicity, etc.)
    - Treatment or intervention for adverse event
    - Patient disposition (e.g. recovered, improved, with sequelae, etc.)
    - Patient outcome (per regulatory definition in CFR 314.80)

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/25/2014

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Costello, Colleen (Colleen.Costello@takeda.com); Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Post-Marketing Commitment Comments (CMC Micro DP) - April 21, 2014
Date:	Monday, April 21, 2014 9:09:04 AM

Hi Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Below please find revised language for the post-marketing commitments requested by the CMC Micro Drug Product Review Team for your BLA for ENTYVIO (vedolizumab). Please confirm your agreement with these requirements and commitments, including agreement with the proposed milestone dates. We request that you provide your response by April 28, 2014, COB.

Microbiology Quality PMC #1

To assess the sensitivity of the current dye and microbial ingress assays for container closure integrity testing. The studies will be conducted by perforating the container closure system with needles and capillaries that vary in internal diameter down to an internal size of (b) (4). If it is determined that the current methods are not sensitive to perforations of (b) (4), the methods will be optimized as necessary for the detection of breaches (b) (4) The target submission of a sensitive method for container closure integrity validation and final report will be 12/31/2014.

Microbiology Quality PMC #2

To conduct studies to qualify the endotoxin kinetic turbidometric LAL assay for testing vedolizumab bulk drug product and finished drug product. Qualification studies will be conducted on three lots of endotoxin-spiked undiluted bulk drug product and finished drug product held under held under worst case hold conditions in the relevant containers. These studies should demonstrate acceptable endotoxin recoveries of spiked endotoxin initially and after worse case hold conditions. Submission of qualified endotoxin kinetic turbidometric 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.

Microbiology Quality PMC #3

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

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/21/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Quinn, Karen (Karen.Quinn@takeda.com); Sundaram, Bagyashree; Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Labeling Comments (PI) - April 17, 2014
Date:	Thursday, April 17, 2014 6:05:17 PM
Attachments:	BLA 125476_PI_FDA_Version_Clean_17APR2014.doc BLA 125476_PI_FDA_Version_Red Lined_17APR2014.doc

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Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Attached please find a clean word copy of the current FDA version of the prescribing information. Please note there are a couple comments, for your attention. We request that you use the clean version for further editing. To facilitate your review, I have also attached the redlined version of the label, with all changes from your prior version of labeling marked with tracked changes.

We request you provide your response by May 02, 2014, COB.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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

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/s/

KEVIN B BUGIN
04/21/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - PMR/PMC Comments (Clinical Lactation Study) - April 15, 2014
Date:	Tuesday, April 15, 2014 2:32:45 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

The Pediatric and Maternal Health Staff wants to convey the following message regarding your submission dated April 14, 2014, in response to our comments on the clinical lactation study.

> The clinical lactation study should be completed in lactating women who are receiving vedolizumab therapeutically based on current approved prescribing information. Lactation must be well-established and weaning must not be underway. The lactation study should encourage continued breastfeeding upon study discontinuation and not increase the likelihood of breastfeeding failures. Breastfeeding should be interrupted only for milk sampling. In our experience the final study report is usually submitted one to three years after protocol approval.

Please respond no later than April 17, 2014, COB.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/15/2014

From: Bugin, Kevin
To: Quinn, Karen (Karen.Quinn@takeda.com)
Cc: Bugin, Kevin; Costello, Colleen (Colleen.Costello@takeda.com)
Subject: BLA 125476 ENTYVIO (vedolizumab) - Pending Information Request (Micro DP) - April 11, 2014
Date: Friday, April 11, 2014 1:50:03 PM

Hi Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

In your April 11, 2014, Amendment response to the Quality Micro Drug Product Question 1 only included a commitment to develop an endotoxin release assay for the drug product. (b) (4) [redacted] Please modify the commitment to include development of an (b) (4) assay for the bulk drug product and include the worst-case hold conditions of the bulk drug product in the relevant containers.

We request you provide your response by Monday, April 14, 2014.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/11/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Pending Information Request - Clinical (Safety Communication) - April 10, 2014
Date:	Thursday, April 10, 2014 2:41:26 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

As previously conveyed, a REMS is not required for this application, however, we recommend implementation of certain elements of your proposed communication plan. Specifically:

- Medication Guide: This is still recommended and should be provided to health care providers to provide to patients at their first infusion, and should be available on the ENTYVIO Website. The language for the medication guide was agreed upon in previous correspondence.

(b) (4)

A (b) (4) is no longer recommended.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
04/10/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Pending Information Request - Clinical Pharmacology (PMC) - April 10, 2014
Date:	Thursday, April 10, 2014 12:10:56 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing your response to our April 01, 2014, Post Marketing Requirements and Commitments Communication and have the following request for more information. Please provide a response to this request by April 14, 2014.

For PMC 20, we acknowledge that you plan to take a step wise approach. However, it is not clear what are the planned steps. Judging from the proposed timeline for protocol submission, it appears that you plan to conduct one study. It is unclear though how you plan to incorporate "the step wise approach" in the proposed study. Please clarify your plan for the step wise approach.

Additionally, we propose the following text rearrangement for the PMC:

> Evaluate in a step-wise approach the disease-drug-drug interaction (Disease-DDI) potential for vedolizumab (b) (4) to indirectly affect the exposure of CYP substrate drugs by modulating pro-inflammatory cytokines in patients with UC and CD who are treated with vedolizumab.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/10/2014

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Costello, Colleen (Colleen.Costello@takeda.com); Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Pending Information Request - Microbial Quality (Drug Product + Drug Substance) - April 03, 2014
Date:	Thursday, April 03, 2014 11:29:12 AM

Hi Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality Information submitted in support of your application and have the following requests for additional information. We request your response by April 10, 2014, COB.

Drug Substance, Microbial Quality

1. Please amend the BLA to reflect the maximum hold times for (b) (4) as stated in (b) (4) submitted in amendment 0071. Maximum hold times for (b) (4) may be extended after validation as per (b) (4)

Drug Product, Microbial Quality

1. Preliminary results were provided for the use of the turbidimetric assay for drug product release using (b) (4) Table 1-2 amendment 125476/0.68). Provide results using the turbidimetric assay (b) (4) If acceptable endotoxin recoveries over time are obtained using (b) (4) implement the turbidometric assay as a drug product release assay and demonstrate method suitability with three drug product lots.

2. If use of (b) (4) results in unacceptable recoveries, conduct studies to fully validate the turbidimetric assay using (b) (4) . This validation study should include a justification for the use of (b) (4) versus other concentrations.

3. You may consider evaluating the feasibility of the gel clot method for drug product release. In general, the gel clot method has been shown to be less prone to low endotoxin recovery problems.

4. As an interim, until a validated and reliable LAL test can be implemented, conduct rabbit pyrogen testing for drug product release.

5. Submit endotoxin specifications for all drug product formulation (b) (4) conduct endotoxin recovery studies with all drug product formulation (b) (4) and submit the results. (b) (4) should be (b) (4) and held

for the maximum hold time. If the study indicates low endotoxin recovery, develop a valid method to measure endotoxin in the (b) (4) Until a new valid method is in place, endotoxin should be established for (b) (4) and maximum hold times (b) (4). Indicate when those activities will be conducted and when the final report will be submitted to the Agency.

6. Submit bioburden data for the three 2 – 8°C and three room temperature bulk hold periods described in the Amendment 125476/0.53 response to Question 2.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
04/03/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Post Marketing Requirements and Commitments Comments - April 01, 2014
Date:	Tuesday, April 01, 2014 4:00:29 PM

Hi Colleen

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Below please find the current list of post-marketing requirements and commitments for your BLA for ENTYVIO (vedolizumab). Please confirm your agreement with these requirements and commitments, including agreement with the proposed milestone dates. Where milestone dates are not provided, please provide us with your proposed dates for completion. We request that you provide your response by April 3, 2014, COB.

PMRs

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

   Final Protocol Submission: September 2014
   Trial Completion: March 2016
   Final Report Submission: March 2017

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

   Final Protocol Submission: September 2016
   Trial Completion: September 2021
   Final Report Submission: September 2022

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

   Final Protocol Submission: September 2016
   Trial Completion: September 2021
   Final Report Submission: September 2022

4. Complete Clinical Trial C13008, an open-label trial to determine the long-term safety of vedolizumab in patients with ulcerative colitis and Crohn's disease. Safety evaluations include

but are not limited to the occurrence of serious infections including progressive multifocal leukoencephalopathy (PML) and malignancies.

Final Protocol Submission: September 2008
Trial Completion: March 2016
Final Report Submission: March 2017

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

   Final Protocol Submission:
   Study Completion:
   Final Report Submission:

6. Conduct 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. Annual interim reports are to be submitted to the Agency.

   Final Protocol Submission:
   Study completion:
   Final Report submission:

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

Final Protocol Submission:
Trial Completion:
Final Report Submission:

PMCs

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

   Final Report Submission: 12/31/2014

9. To add osmolality testing to vedolizumab drug product lot release specifications after qualification of the analytical procedure and sufficient data becomes available to set an acceptance criterion.

   Final Report Submission: 9/30/2014

10. To add polysorbate 80 testing to vedolizumab drug product release specifications after qualification of the analytical procedure and sufficient data become available to set an acceptance criterion.

    Final Report Submission: 12/31/2014

11. To implement a validated non-reducing SDS-based method for quantitative evaluation of size-related impurities in vedolizumab drug substance and drug product release and stability specifications after sufficient data become available to set an acceptance criterion.
    Final Report Submission: 2/29/2016

12. 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.

    Final Report Submission: 12/31/2014

13. 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.

    Final Report Submission: 12/31/2014

14. To develop, validate and implement a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential host cell proteins compared to the current assay for vedolizumab drug substance lot release.

    Final Report Submission: 12/31/2017

15. To reassess vedolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale to allow for better statistical analysis.

    Final Report Submission: 12/31/2016

16. To reassess vedolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale to allow for better statistical analysis.

    Final Report Submission: 12/31/2018

17. To conduct a maximum hold time study for the formulated drug substance using representative containers by July 2014. If low endotoxin recovery is found in the formulated drug substance during the maximum hold time study, either hold times will be reevaluated or an alternative method to measure endotoxin in formulated drug substance will be developed and validated by December 31, 2014.

    Final Report Submission: 12/31/2014

18. To verify the endotoxin recovery results for the (b) (4) and establish action limits for this solution once the results are confirmed by a validated method. If low endotoxin recovery is found, maximum hold times (b) (4). The activities associated to this commitment will be completed and the final report will be submitted on or before 31 December 2014.

    Final Report Submission: 12/31/2014

19. 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.

    Final Protocol Submission:
    Study Completion:
    Final Report Submission:

20. Evaluate 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 UC and CD who are treated with vedolizumab.

Final Protocol Submission:
Study Completion:
Final Report Submission:

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
04/01/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Clinical/Safety - April 01, 2014
Date:	Tuesday, April 01, 2014 3:54:37 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Clinical/Safety information submitted in support of your application and have the following requests for more information. Please provide a response to this request by April 10, 2014.

1. Please provide an estimate of the proportion of vedolizumab-exposed subjects who would start vedolizumab without trying a TNF-α inhibitor first. If you anticipate any proportion changing over time, please provide year-by-year estimates of proportions.
2. Please provide an estimate of the proportion of vedolizumab-exposed subjects who would start vedolizumab without trying natalizumab first. If you anticipate any proportion changing over time, please provide year-by-year estimates of proportions.
3. Please provide an estimate of the proportion of vedolizumab-exposed subjects that would be on vedolizumab for an indication for ulcerative colitis vs. Crohn's disease. If you anticipate any proportion changing over time, please provide year-by-year estimates of proportions.
4. Please provide an estimate of the proportion of vedolizumab-exposed subjects that would be on vedolizumab for an indication for ulcerative colitis vs. Crohn's disease, stratified by VDZ users on drug as 2nd vs. 3rd line therapy. If you anticipate any proportion changing over time, please provide year by-year estimates of proportions.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
04/01/2014

From: Bugin, Kevin
To: Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Clinical - March 21 2014
Date: Friday, March 21, 2014 7:39:42 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Clinical information submitted in support of your application and have the following requests for more information. Please provide a response to this request by March 28, 2014.

1. Provide the median (minimum, maximum) time to loss of clinical remission by treatment group (PBO and VDZ Q8W) to produce a table like the one below for the following groups (include the number of patients [n]):
   - Patients in Clinical Remission at Week 6
   - Patients in Clinical Remission at Week 6 that met the endpoint of Clinical Remission at Week 52
   - Patients in Clinical Remission at Week 6 that met the endpoint of "Durable Clinical Remission" (i.e., Clinical Remission at 11 of 13 visits)

Group	Time to Loss of Clinical Remission*	
	PBO	VDZ Q8W
Patients in Clinical Remission at Week 6	Median (min, max), n	Median (min, max), n
Patients in Clinical Remission at Week 6 that met the endpoint of Clinical Remission at Week 52	Median (min, max), n	Median (min, max), n
Patients in Clinical Remission at Week 6 that met the endpoint of "Durable Clinical Remission"	Median (min, max), n	Median (min, max), n

*Time measured in weeks (where Week 0 is start of induction phase and Week 6 is start of maintenance phase) to the visit when the patient was not in clinical remission.

2. For the patients in Clinical Remission at Week 6 that met the endpoint of Clinical Remission at Week 52 but did <u>not</u> meet the endpoint of "Durable Clinical Remission", provide the following by treatment group (VDZ Q8W or PBO):

   a. Profile (by individual patient) of which visits the patient was/was not in clinical remission to produce a table like the one below:

Pt ID#	Visits* during which the Patient was in Clinical Remission [Week]												
	6	10	14	18	22	26	30	34	38	42	46	50	52
...	X	·	X	·	X	·	·	·	X	X	·	·	X

*Clinical Remission at a visit indicated by "X"; not in clinical Remission indicated by "·"

#Identify the treatment group (VDZ Q8W or PBO)

   b. Summary table (of the data in a. above) showing the distribution of the number of patients <u>not</u> in clinical remission at one or more visits between Weeks 10 and 50 (inclusive) by the

number of visits that they were not in clinical remission (i.e., between 1 and 11 visits) (see example table below).

Treatment Group	No. Pts (% of Total[§]) by No. of Visits Not in Clinical Remission										
	1	2	3	4	5	6	7	8	9	10	11
VDZ Q8W	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
PBO	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

*Total number of patients in Clinical Remission at Week 6 that met the endpoint of Clinical Remission at Week 52 but did not meet the endpoint of "Durable Clinical Remission" (in each treatment group - VDZ Q8W or PBO)

c. Profile (by individual patient) of which visits the patient met the following specific definitions for selected CDAI components (i.e., liquid/soft stools; and abdominal pain) to produce a table like the one below:
   - Liquid/Soft Stools: Total number of liquid/soft stools of ≤ 10 for the 7 days prior to the visit
   - Abdominal Pain: Daily abdominal pain score of ≤ 1 for the 7 days prior to the visit

   Also, provide the data in a. above again for ease of comparison.

Pt ID[‡]	Definition	Visits[§] during which the Patient met Definition [Week]												
		6	10	14	18	22	26	30	34	38	42	46	50	52
…	Clinical Remission*	X	·	X	·	X	·	·	·	X	X	·	·	X
	Liquid/Soft Stools[#]	X	·	·	·	·	·	X	·	X	·	X	·	X
	Abdominal Pain[†]	X	X	X	·	·	·	·	·	·	X	·	·	X

[§]Met definition at a visit indicated by "X"; did not meet definition at a visit indicated by "·"

[‡] Identify the treatment group (VDZ Q8W or PBO)

*Clinical Remission definition based on CDAI

[#]Total number of liquid/soft stools of ≤ 10 for the 7 days prior to the visit

[†]Daily abdominal pain score of ≤ 1 for the 7 days prior to the visit

d. Summary table (of the data in c. above) showing the distribution of the number of patients in the following categories at one or more visits between Weeks 10 and 50 (inclusive) by the number of visits (i.e., between 1 and 11 visits) (see example table below):
   - did not meet the definition of clinical remission, did not meet the definition of liquid/soft stools, and did not meet the definition of abdominal pain
   - did not meet the definition of clinical remission, but met both the definition of liquid/soft stools and the definition of abdominal pain

Category based on Definitions Met / Not Met	Treatment Group	No. of Pts (% of Total[§]) by No. of Visits										
		1	2	3	4	5	6	7	8	9	10	11
• Clinical Remission* NOT met;	VDZ Q8W	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

• Liquid/Soft Stools# NOT met; and • Abdominal Pain† NOT met	PBO	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
• Clinical Remission* NOT met; • Liquid/Soft Stools# MET; and • Abdominal Pain† MET	VDZ Q8W	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	PBO	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

§Total number of patients in Clinical Remission at Week 6 that met the endpoint of Clinical Remission at Week 52 but did not meet the endpoint of "Durable Clinical Remission" (in each treatment group - VDZ Q8W or PBO)

*Clinical Remission definition based on CDAI

#Total number of liquid/soft stools of ≤ 10 for the 7 days prior to the visit

†Daily abdominal pain score of ≤ 1 for the 7 days prior to the visit

e. Brief discussion of the CDAI components that resulted in criteria for clinical remission based on CDAI not being met (at multiple visits) particularly in those patients that met the definitions for liquid/soft stools and abdominal pain as described above.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
03/21/2014

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Costello, Colleen (Colleen.Costello@takeda.com); Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Post Marketing Commitment Comments - Quality Micro (Drug Substance) - March 05, 2014
Date:	Wednesday, March 05, 2014 5:19:46 PM

Hi Karen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

In amendment 0064 Takeda agreed:

- To conduct a maximum hold time study for the formulated drug substance using representative containers by July 2014. If low endotoxin recovery is found in the formulated drug substance during the maximum hold time study, either hold times will be reevaluated or an alternative method to measure endotoxin in formulated drug substance will be developed and validated by December 31, 2014.

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

Can you confirm that you agree with the above wording. This text will become the final text for these PMCs. And for the second commitment above, can you provide us with the time of completion and when final report will be submitted.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
03/05/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Labeling Comments (PI+MC) - February 28, 2014
Date:	Friday, February 28, 2014 7:36:20 PM
Attachments:	BLA125476_PI_FDA Version 3_28Feb2014_Clean.docx BLA125476_PI_FDA Version 3_28Feb2014_Redlined.docx BLA125476_MG_FDA Version 3_28Feb2014_Clean.docx BLA125476_MG_FDA Version 3_28Feb2014_Redlined.docx

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Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Attached please find a clean word copy of the current FDA version of the prescribing information and medication guide. Please note there are comments throughout, for your attention. Please use these versions for further editing. To facilitate your review, I have also attached the redlined versions of the label and medication guide, with all changes from your prior version of labeling marked with tracked changes. The formatting is very muddled and it can be confusing to read, which is why we request you use the clean versions for further editing.

We request you provide your response by Noon on March 11, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
02/28/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 ENTYVIO (vedolizumab) - Pending Information Request - Clinical - February 28, 2014
Date:	Friday, February 28, 2014 7:36:12 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical information submitted in support of your application and have the following request for information.

> **In Study C13006, present (by treatment group) the proportion of patients that met the endpoint of "durable clinical remission" in the subgroup of patients that were in clinical remission at Week 6; include p value, treatment difference, and 95% CI.**

We request you provide your response by Noon on March 11, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
02/28/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Statistics - February 19, 2014
Date:	Wednesday, February 19, 2014 12:44:37 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical and statistics information submitted in support of your application and have the following request for more information.

1. Please clarify the discrepancy of number of vedolizumab patients who were Week 6 responders in the Induction Phase in Cohort 1 given in Table 14.3.1.32A of the CSR and in the Open Label Cohort 2 given in Table 39.31.1.1, (Response to Agency Questions dated October 18) (99 in Cohort 1 and 355 in Cohort 2) and number of patients who were randomized in the Maintenance Phase given in Figure 3-1(C13007 FESA) (96 in Cohort 1 and 365 in Cohort 2).

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
02/19/2014

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Quality (Drug Product, Micro) - February 7, 2014
Date:	Friday, February 07, 2014 11:45:15 AM

Hi Colleen and Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality information submitted in support of your application and have the following requests for more information.

1. Regarding your Amendment 125476/0.58 response concerning endotoxin detection in Vedolizumab drug product:

a) Submit the endotoxin testing protocol and summary data for all conditions tested. Include the spike concentration, sampling time points, recovery concentrations, and percent recovery values.

b) Submit data from LAL assays that incorporate (b) (4) to demonstrate adequate endotoxin recoveries from the following:
   i) Drug product formulation (b) (4) held for the maximum hold time in the containers to be used for commercial production.
   ii) Vialed drug product held for a period that encompasses the maximum time allowed between sample preparation and testing.

2. The Amendment 125476/0.53 response to Question 1 states that endotoxin testing for drug product (b) (4) was only conducted to establish hold time limits, and that testing is not routinely performed during production. Please implement routine endotoxin testing for these (b) (4) The endotoxin limit should be based on process capability and product quality impact.

3. The Amendment 125476/0.53 response to Question 3 states that shipping validation data for transport from (b) (4) to (b) (4) and from (b) (4) to specialty distribution centers would be provided by 1/31/2014. Please submit the data.

We request your response by February 28, 2014.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager

Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
02/07/2014

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Quality (Drug Substance, Micro) - February 7, 2014
Date:	Friday, February 07, 2014 9:04:51 AM

Hi Colleen and Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

According to amendment #0056 submitted on January 16, 2014 your studies with reconstituted drug product are indicative of low endotoxin recovery when spiked with endotoxin standard.

1. Conduct low endotoxin recovery studies using [redacted] (b) (4) formulated drug substance spiked with known amounts of endotoxin standard and holding it the maximum hold time and submit study report to the Agency. The studies should be conducted using the validated drug substance LAL method and containers of similar composition as those used for drug substance during hold.
2. If low endotoxin recovery is found in formulated drug substance, develop a valid method to measure endotoxin in formulated drug substance and submit path forward for the development of the new method.
3. Conduct routine endotoxin testing for the [redacted] (b) (4) solution added to the [redacted] (b) (4) formulated without [redacted] (b) (4) and submit endotoxin action limit.

We request your response by February 20, 2014.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
02/07/2014

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	RE: BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Post Marketing Commitment Comment - February 3, 2014
Date:	Monday, February 03, 2014 9:48:07 PM

Hi Karen and Colleen,

I apologize. I just realized that the CMC team asked for a response by next Monday, February 10, 2014.

Regards,
Kevin

From: Bugin, Kevin
Sent: Monday, February 03, 2014 9:47 PM
To: Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Post Marketing Commitment Comment - February 3, 2014

Hi Colleen and Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

In regard to the PMC 4 (nr-SDS-PAGE assay) and PMC 7 (host cell protein assay) your proposed time line for submitting the final reports for these PMCs are approximately 3 and 4 years respectively. Based on our experience, your proposed timeline seems unreasonably long for fulfillment of PMC 5 and 7. Revise your timeline for fulfillment of PMC 5 and 7, or provide justification for your proposed timeline to fulfill these PMCs.

We request your response by February 21, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
02/03/2014

From: Bugin, Kevin
To: Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Safety - January 23, 2014
Date: Thursday, January 23, 2014 9:30:57 AM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the safety and post-marketing information submitted for your application and have the following requests for information. Please respond to request number 3 by January 31, 2014.

1. Submit a Pharmacovigilance Plan, if available, designed to detect new safety risks and to further evaluate identified safety risks with vedolizumab following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). Please include the Pharmacovigilance Plan in the BLA application in the appropriate module so it can be reviewed accordingly.

2. Provide an Enhanced Pharmacovigilance Plan (EPV) for Infections and Liver Injury which include the following components:

   - expedited reporting (15 days) regardless of seriousness, report source, or labeling status

   - targeted questionnaire/checklist to actively inquire reporters for additional case information

   - protocol for bi-annual periodic postmarket safety assessment of new and cumulative safety information

3. Please provide summary exposure statistics as of 12/26/2013 using the following table:

		All Patients Exposed to Vedolizumab (N =3,326)	**All Patients Exposed to Vedolizumab w/ RAMP* (N =2,830)**
No. of Infusions	Mean (SD)		
	Median (Min-Max)		
No. of Infusions with > 28 days	Mean (SD)		
	Median (Min-		

FU	Max)		
No. of Months Exposure	Mean (SD)		
	Median (Min-Max)		

FU=follow-up; SD=standard deviation; Min=minimum value; Max=maximum value
*Assessed with at least one subjective checklist in RAMP

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
01/23/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Safety - January 17, 2014
Date:	Friday, January 17, 2014 1:46:46 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the post-marketing study protocol to evaluate the long-term safety of vedolizumab submitted for your application and have the following requests for information.

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.

5) Please provide a clear description of projected open-label study sample size over time. Include assumptions used. Provide a graph showing, over time, projections of subjects with at least 24 months vedolizumab exposure. If you use different attrition rates, support them with a historical attrition data table.

We request that you respond to requests 1a, 1b and 5 by January 27, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
01/17/2014

From: Bugin, Kevin
To: Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Clinical - January 17, 2014
Date: Friday, January 17, 2014 8:47:41 AM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We have the additional Information Request (IR) item below that is related to our IR Item #2 (in the IR dated August 19, 2013) and your response to that IR item (see Page 11 of your Response to IR dated September 9, 2013). IR item #2 stated:

> "Studies C13007 and C13011: Provide as an exploratory analysis by treatment group the proportion of patients in clinical remission at Week 6 (Study C13007), the proportion of patients in clinical remission at Week 52 (Study C13007), the proportion of patients in clinical remission at Week 6 in the TNFα antagonist failure subpopulation (Study C13011), and the proportion of patients in clinical remission at Week 6 in the entire study population (Study C13011) based on the following alternate definition of clinical remission (using daily patient diary data collected for calculation of the CDAI; patients must meet both criteria below):
>
> - Total number of liquid/very soft stools of ≤ 10 in the relevant week; and
> - Abdominal pain rated as 0 or 1 for each day in the relevant week."

In your response, you provided the proportion of patients (at each of the requested time points and in each of the requested study populations) that met both these criteria ***and CDAI ≤ 150***.

1. We request that you provide the proportions of patients by treatment group that met both the above criteria ***regardless of CDAI score*** (i.e., met the criteria for the "**alternate definition of clinical remission**")(for each of the following study populations at each of the following time points):
   - C13007 - Week 6
   - C13007 - Week 52
   - C13007 - ***both*** Week 6 and Week 52 (note that this was not requested in the original IR)
   - C13011 TNFα Antagonist Failure Population - Week 6
   - C13011 Entire Study Population - Week 6

   The table you provide should look substantially like the following:

Table 1. Proportions of Patients that Met Criteria for the Alternate Definition of Clinical Remission* by Study and Visit

Study / Population	Visit	Vedolizumab	Placebo
C13007	Week 6	n/N (%)	n/N (%)
C13007	Week 52	n/N (%)	n/N (%)
	Both Weeks 6 and		

C13007	52#	n/N (%)	n/N (%)
C13011 TNFα Antagonist Failure Population	Week 6	n/N (%)	n/N (%)
C13011 Entire Study Population	Week 6	n/N (%)	n/N (%)

*Alternate Definition of Clinical Remission: Total number of liquid/very soft stools of ≤ 10 in the 7 days prior to the visit; and abdominal pain rated as 0 or 1 for each day in the 7 days prior to the visit.

#Met criteria for the alternate definition of clinical remission at ***both*** Week 6 and Week 52

Please provide your response to this request by January 31, 2014.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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KEVIN B BUGIN
01/17/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Labeling Comments (PI+MG) - January 14, 2014
Date:	Tuesday, January 14, 2014 11:30:04 AM
Attachments:	BLA 125476 - Entyvio (vedolizumab) - USPI - FDA Version 2 - 14Jan2014.doc BLA 125476 - Entyvio (vedolizumab) - MG - FDA Version 1 - 14Jan2014.doc

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Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Attached please find an MS Word document containing the Agency's revisions to the Prescribing Information for Entyvio. Also, attached is a separate document containing revisions to the Medication Guide. Please review and provide us with your response by January 22, 2014. If you are unable to meet this timeline, please contact me to discuss.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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

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KEVIN B BUGIN
01/14/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com); Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - CMC (Micro DP) - January 13, 2014
Date:	Monday, January 13, 2014 5:25:19 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the CMC information for your product and have the following comments and requests. We request that you provide your response as soon as possible.

> The Amendment 125476/0.43 response to Question 5 states that the method sensitivity limits for the dye and microbial ingress assays will be determined by perforating the container closure system with needles and capillaries that vary in internal diameter down to an internal size of ≤ (b) (4) and that a more sensitive assay will be developed if perforations of (b) (4) are not detectable by the current methods. The response also states that the studies will be completed by June, 2014. As this timeframe is beyond the PDUFA goal date, please submit a post-marketing commitment (PMC) for study performance. The commitment should include a proposal to develop an assay capable of detecting perforations (b) (4) using Vedolizumab drug product units breached through their stoppers with needles and capillaries capillaries as stated in Amendment 125476/0.43, and include times for the following milestones: final protocol submission date; study/trial completion date; final report submission date.

If you have any questions, please do not hesitate to contact me.

Kind regards,

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
P-301-796-2302

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/s/

KEVIN B BUGIN
01/13/2014

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Safety - January 06, 2014
Date:	Monday, January 06, 2014 1:10:42 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

Submit, by close of business on January 10, 2014, an updated vedolizumab exposure table stratified by months of exposure and number of infusions cumulative to December 27, 2013 (i.e., a 6 month update to Table 35, 120 day safety update).

If you have any questions, please do not hesitate to contact me.

Kind regards,

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
01/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476/0

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Entyvio (vedolizumab).

On December 06, 2013, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 20, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017."

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
12/23/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Carton and Container Comments - December 04, 2013
Date:	Wednesday, December 04, 2013 10:01:10 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the carton and container labeling for your product and have the following requests. We request that you provide your response as soon as possible.

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. 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 any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/04/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Clinical - December 03, 2013
Date:	Tuesday, December 03, 2013 12:21:33 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Clinical information for your product and have the following requests for information. We request that you provide your response as soon as possible.

Please clarify the definition of "baseline concomitant immunosuppressant use" used in the exploratory subgroup analyses for the primary and secondary endpoints (Section 7.3.3 of Integrated Summary of Safety). Specifically, were patients in the US who were on concomitant immunosuppressants for ≤ 6 weeks categorized as patients "with concomitant immunosuppressant use" for maintenance study results?

Please clarify the definition for US protocol criteria status used for the FDA requested post hoc analyses (Page 9 of response to request for information, submitted August 21, 2013), specifically:

- For the induction study endpoints, did you include a requirement that patients had discontinued immunosuppressants by Week 6, or was this defined merely as patients who had failed immunosuppressants and/or anti-TNF agents (excluding corticosteroid only failures)?
- For the Maintenance Study endpoints, did you include a requirement for both prior treatment failure (as described above) and that patients had discontinued immunosuppressants by Week 6?

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
12/03/2013

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending Information Request - Quality (micro) - December 03, 2013
Date:	Tuesday, December 03, 2013 9:56:02 AM

Hi Colleen and Karen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality information for your product and have the following requests for information. We request that you provide your response as soon as possible.

1. Insufficient justification was provided for the endotoxin acceptance criterion of (b) (4) for drug product (b) (4). Please submit a criterion that is in line with process capability. You should also consider using a (b) (4) that permits a higher sensitivity limit for the endotoxin method.

2. Insufficient justification was presented for not having a hold time limit for the bulk drug product. Please establish a limit based on the shortest of the three longest bulk periods used for commercial scale manufacture.

3. The Amendment 125476/0.37 response to Question 14 did not provide sufficient details regarding the procedures, acceptance criteria and data for shipping validation. Please submit the following:
   a. A detailed description of the packaging configuration to be used for shipment from (b) (4) packaging site, and from (b) (4) to the distribution centers. In your response include the (b) (4)
   b. A detailed description of how the drug product is to be shipped (b) (4) from (b) (4), and from (b) (4) to the distribution centers. In your response include the distance, and approximate shipping time for each of the transportation routes.
   c. The procedures used for (b) (4) during shipping validation, including the locations of the (b) (4)
   d. Temperature data for shipping validation conducted under normal and worst case (summer and winter) conditions. In your response include how worst case conditions were tested.

4. During stability testing the container closure integrity test provides for a better assessment of maintenance of microbiology quality than the sterility test. For the post-marketing stability protocol presented in Table 1-1 of Module 3.2.P.8.2.1.2, it is recommended that the container closure integrity test in lieu (b) (4) be performed. The test should be performed at annual intervals and at expiry (0, 12, 24, 36, 48, and 60 months) on

stability samples stored at 5°C/ambient RH storage conditions.

5. Your 11/20/2013 Amendment 125476/0.43 responses to Questions 1 and 2 do not state how the method sensitivity limits for the dye and microbial ingress assays will be determined, and when the results will be reported. Studies and data supporting the limits should be provided to the Agency no later than mid-January, 2014. If this is not possible, please submit a post-marketing commitment for study performance.

6. Your 11/20/2013 Amendment 125476/0.43 response to Question 3 did not state when the results for endotoxin recovery will be reported. The results should be reported to the Agency no later than mid-January, 2014. If the results reveal evidence of low endotoxin recovery, a path forward must be determined for measuring pyrogen in the finished drug product at release.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
12/03/2013

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Quality - November 21, 2013
Date:	Thursday, November 21, 2013 3:12:12 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality information for your product and have the following requests for information. We request that you provide your response as soon as possible. If clarification is needed, please contact us to schedule a teleconference.

1. Regarding statistical methods used as part of determining specification acceptance criteria, (b) (4) are not generally considered appropriate, as was discussed during the November 13, 2012 pre-BLA meeting. In addition, the use of data from materials generated using the previous manufacturing processes may not be appropriate for these calculations, since this analysis provides an expectation that is linked to the manufacturing process. Therefore, statistical analyses targeting process capability lead to acceptance criteria ranges that are tighter than those that were initially proposed. These analyses are not the only factors that should contribute to the acceptance criteria for lot release and stability studies; the in vitro potencies of the materials used in clinical studies should also be considered. The range for % binding activity, from all batch analyses data (Process A, B and C), is (b) (4) for drug substance and (b) (4) for drug product, with the exception of one outlying value that appears to be related to the assay and not the potency of the drug product. The range for potency measured using the adhesion assay, from all batch analyses data (Process A, B and C), is (b) (4) for drug substance and (b) (4) for drug product. The proposed acceptance criteria of (b) (4) relative to reference standard" for the binding and adhesion assays for drug substance and drug product lot release and stability do not reflect the historical experience of the in vitro potency of the vedolizumab materials used in the phase 1, 2 and 3 clinical trials. Given the magnitude of the difference between the lower end of the proposed acceptance criteria and the clinical experience, combined with the results from statistical analyses demonstrating the capability of the manufacturing process, the acceptance criteria for the potency assays (binding and adhesion) for vedolizumab drug substance and drug product lot release and stability specifications should be tightened to (b) (4) relative to reference standard."

2. Because the potency of DS and DP is measured against the reference standard (RS), it is important to provide adequate control over the potency of the RS during. The current proposed acceptance criteria for the January 2014 RS requalification (b) (4) relative to reference standard and mean EC_{50} is within ± 3 SD of mean historical

EC_{50} results of primary reference standard; response to questions received November 8, 2013) do not provide sufficient control over the potency of the reference standard to prevent drift in the quality of the reference standard and subsequently, the drug product, over time. The mean of the RS results through the course of its use is not an appropriate comparator for requalification of the RS, since the results over time would capture any changes in RS; the current potency of the RS should be compared to the initial potency. Revise the acceptance criteria for the potency assays for the January 2014 RS requalification to reflect a requirement that the results be sufficiently similar to the potency values obtained at the time of the initial qualification of the RS. The current potency of the RS should be significantly tighter than (b) (4) of the original value.

3. The commercial assay for measuring host cell protein (HCP) was used to release materials used in the clinical trials. In the BLA, Takeda proposes to use an (b) (4) measuring HCP; however, the data provided to support its use are not sufficient to demonstrate that the new assay is better than (or equivalent to) the commercial assay. (b) (4) (b) (4)

   While these changes may not be significant enough to trigger an out of specification result, they may appear as an out of trend result. Therefore, we prefer that the HCP level in the commercial vedolizumab drug substance be measured using the commercial assay that will maintain a consistent measure as compared to the material used in the clinical studies. We agree with the specification acceptance criterion proposed in the response to question H2b in the responses to the questions received November 8, 2013.

4. We note that the release and stability specifications were updated to include the adhesion assay; however the stability protocols were not revised. Given that one of the reasons for inclusion of the adhesion assay is its stability indicating properties, this assay should be included in the post-approval stability protocols. Update the drug substance and drug product protocols to include the adhesion assay as a test method for the potency.

5. We note that the drug substance release specifications listed in the (b) (4) protocols for the (b) (4) and the (b) (4) do not reflect the updated commercial drug substance release specifications. Revise the reprocessing protocols for the (b) (4) and (b) (4) with the updated commercial vedolizumab drug substance batch release specifications.

6. Biologic product drug substances are given expiry periods, rather than retest periods. Update the BLA to reflect that drug substance has an expiry period.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
11/21/2013

Executive CAC

Date of Meeting: November 19, 2013

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Dan Mellon, Ph.D., OND IO, Member
Sushanta K. Chakder, Ph.D., DGIEP, Supervisory Pharmacologist
Tamal Chakraborti, Ph.D., DGIEP, Presenting Reviewer

Author of Draft: Tamal Chakraborti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

BLA#: 125476
Drug Name: Vedolizumab (MLN0002, Entyvio®)
Sponsor: Takeda Pharmaceuticals U.S.A., Inc.

Background:

MLN0002 (Vedolizumab/LDP-02/Entyvio®) is an IgG1 humanized monoclonal antibody (mAb) indicated for the treatment of adult ulcerative colitis (UC) and Crohn's Disease (CD). MLN0002 is a selective integrin antagonist that binds to α4β7 integrin. MLN0002 does not bind to α4β1 or αEβ7 integrin. MLN0002 inhibits the leukocyte trafficking into the area of intestinal inflammation by selectively antagonizing binding of α4β7 to its ligand, MAdCAM-1. MLN0002 does not antagonize adhesion interactions of α4β1 to its ligand, vascular cell adhesion molecule-1 (VCAM-1). This selective antagonism of α4β7 by MLN0002 restricts inhibition of α4β7/MAdCAM-1 and α4β7/fibronectin pathways resulting in inhibition of migration of leukocytes into GI mucosa, and is therefore expected to reduce inflammation in the GI tract.

Conventional carcinogenicity studies (i.e., rodent bioassays) have not been conducted with MLN0002 to assess its carcinogenic potential as it lacks pharmacological activity in mice and rats. MLN0002 bound with similar affinity to leukocytes from rabbits, monkeys, and humans, but not from mice, rats, or guinea pigs. Rodents are not considered pharmacologically relevant species for MLN0002. However, carcinogenic potential of Act-1 (murine homologue of MLN0002) was assessed in an *in vitro* study (Report RPT-01335) using human tumor cells (RPMI 8866 cell line derived from a human B-cell lymphoma) that expressed α4β7 integrin. In this study, Act-1 did not stimulate the growth or cellular proliferation of RPMI 8866 human B-cell lymphoma cell line that expresses the α4β7 integrin. MLN0002 also did not affect other factors that could affect oncogenesis, such as cytokine production from, or activation or proliferation of primary human leukocytes expressing the α4β7 integrin. In addition, there was no evidence of systemic immunosuppression in repeat dose toxicology studies.

Executive CAC Recommendations and Conclusions:

- The Committee concurred that no conventional 2-year bioassays are needed for vedolizumab.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DGIEP
/SChakder, DGIEP
/TChakraborti, DGIEP
/RPM/KBugin/DGIEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
11/20/2013

DAVID JACOBSON KRAM
11/21/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Clinical - November 19, 2013
Date:	Tuesday, November 19, 2013 12:13:03 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Clinical information for your product and have the following requests for information. We request that you provide your response by November 29, COB.

Please provide all available information on the two potential cases of autoimmune hepatitis:

- C13006-28007-605
- C13006-42016-609

Specifically, we would like a clinical summary on these patients, including labs and concomitant medications, from the time of enrollment in the relevant study to the most recent follow-up. In addition, please provide information on any additional cases of hepatitis or liver injury where drug induced or autoimmune hepatitis were considered in the differential.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
11/19/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	RE: BLA 125476/125507 - Entyvio (vedolizumab) - Labeling Comments - November 15, 2013
Date:	Friday, November 15, 2013 7:35:30 PM
Attachments:	BLA 125476-125507_Entyvio_USPI_FDA Version 1_Red Lined.doc

Hi Colleen,

As I mentioned on the phone earlier, some sort of glitch occurred during the publishing/preparation of the MS Word file I sent earlier today. Please use the attached version of labeling for review. I apologize for any confusion.

If you have any questions as the team goes through the revisions, please let me know.

Thanks,
Kevin

From: Bugin, Kevin
Sent: Friday, November 15, 2013 2:47 PM
To: Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Bugin, Kevin
Subject: BLA 125476/125507 - Entyvio (vedolizumab) - Labeling Comments - November 15, 2013

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are communicating our revisions to the Prescribing Information for vedolizumab. Please note that these revisions should not be considered final, and further revisions should be expected. Multiple labeling consultants continue to review the PI and patient counseling components of the labeling. Furthermore, depending on the outcomes of the December 09, 2013, Advisory Committee Meeting, additional revisions could occur.

Attached please find a MS Word document with the revisions in tracked changes.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER

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KEVIN B BUGIN
11/25/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 - Entyvio (vedolizumab) - Labeling Comments - November 15, 2013
Date:	Friday, November 15, 2013 2:47:10 PM
Attachments:	BLA 125476-125507_Entyvio_USPI_FDA Version 1_15Nov2013_Red Lined.doc

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are communicating our revisions to the Prescribing Information for vedolizumab. Please note that these revisions should not be considered final, and further revisions should be expected. Multiple labeling consultants continue to review the PI and patient counseling components of the labeling. Furthermore, depending on the outcomes of the December 09, 2013, Advisory Committee Meeting, additional revisions could occur.

Attached please find a MS Word document with the revisions in tracked changes.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
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/s/

KEVIN B BUGIN
11/15/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com); Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 1255476/125507 Entyvio (vedolizumab) – Post-marketing Commitment Comments - November 15, 2013
Date:	Friday, November 15, 2013 1:29:39 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are communicating a preliminary list of post-marketing commitments identified by the FDA review team to date. We request that you provide your response by December 02, COB.

Furthermore, pending the outcomes of the December 09, 2013, Advisory Committee meeting, additional Post-marketing Requirements and/or Commitments may be communicated. This list does not constitute a final list of post-approval requirements and/or commitments.

Quality:

PMC 1 To perform additional testing or procedures to confirm the monoclonality of the MCB.

PMC 2 [redacted] (b) (4)

PMC 3 To implement testing and quantitative acceptance criteria for osmolality and polysorbate 80 in the vedolizumab drug product lot release program.

PMC 4 To develop a non-reducing SDS-based assay that is capable of providing quantitative data assay for evaluation of size-related impurities. This assay will be implemented in the release and stability programs for vedolizumab DS and DP after sufficient data to set an appropriate acceptance criterion have been acquired.

PMC 5 To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to vedolizumab, including procedures for accurate detection of binding antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC 6 To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to vedolizumab, including procedures for accurate detection of neutralizing antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC 7 To develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential host cell

contaminants compared to the current assay. This assay will replace the HCP assay currently being used in the drug substance release program.

PMC 8 To perform a reassessment of vedolizumab drug substance and drug product lot release and stability specifications when a sufficient number of DS and DP lots (e.g., ≥ 30) have been manufactured at the commercial scale.

PMC 9 (b) (4)

Clinical Pharmacology:

PMC 10 A study to reanalyze banked immunogenicity serum samples from ulcerative colitis trial C13006 and Crohn's disease trial C13007 to determine the presence of anti-drug antibodies (ADA) using an improved ADA assay format with reduced sensitivity to product interference. This recommendation is based on the finding of inadequate assessment of immunogenicity incidence in the current BLA.

PMC 11 Evaluate the disease-drug-drug interaction (DDDI) potential between vedolizumab and other CYP substrates. This recommendation is based on the current understanding that CYP enzymes expression is suppressed by inflammatory cytokines associated with inflammatory conditions, and they can normalize upon improvement of the inflammatory conditions. We recommend a step-wise approach. For instance, one can conduct a study to first define the impact of UC or CD, an inflammatory disease condition, on the exposure of CYP substrate drugs (i.e., the disease drug interaction). Such study may involve evaluating the exposures of CYP substrate drugs in healthy subjects and in subjects with severe UC or CD disease. In the event that the disease drug interaction is deemed clinically meaningful, the impact of vedolizumab treatment on observed disease drug interaction as measured by the exposure of CYP substrate drugs can be further evaluated in a subsequent study to evaluate the DDDI.

Clinical:

PMC 12 Conduct a milk-only lactation trial in lactating women receiving vedolizumab therapeutically to assess concentrations of vedolizumab in breast milk using a validated assay in order to appropriately inform the Nursing Mother's subsection of labeling.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
11/15/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com); Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Quality (micro - drug substance) - November 14, 2013
Date:	Thursday, November 14, 2013 11:53:31 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality information for your product and have the following requests for information. We request that you provide your response by November 21, COB.

The following information should be updated in the BLA to reflect current conditions:

- Section 3.2.S.2.2 of the BLA should be updated to include microbial quality (b) (4) action limits and sample volumes.
- Section 3.2.S.2.5 of the BLA should be updated to include correct Table 9-2 reflecting "Drug Substance (b) (4) performance test".

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
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/s/

KEVIN B BUGIN
11/14/2013

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Quality (micro) - November 13, 2013
Date:	Wednesday, November 13, 2013 7:53:08 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality information for your product and have the following requests for information. We request that you provide your response by November 20, COB.

1) Regarding validation of container closure integrity by the dye ingress method:
   a) Submit the method sensitivity limit (minimum detectable perforation diameter).
   b) Submit the time of dye exposure and the concentration of the dye.
   c) Submit the time and strength of pressure and vacuum application during dye exposure.
   d) The [redacted] (b) (4) for a rigorous validation of container system integrity from a microbial perspective. The positive controls should contain perforations consistent with the method sensitivity limit.

2) Regarding validation of container closure integrity by the microbial ingress method:
   a) Submit the method sensitivity limit (minimum detectable perforation diameter)
   b) Submit the time and strength of [redacted] (b) (4) application during microbial exposure.
   c) The [redacted] (b) (4) for a rigorous validation of container system integrity from a microbial perspective. The positive controls should contain perforations consistent with the method sensitivity limit.

3) The Vedolizumab drug product formulation contains excipients (e.g. polysorbate) that could result in low endotoxin recovery (LER) (see K.L. Williams, Endotoxin Test Concerns of Biologics, *American Pharmaceutical Review*, October 28, 2013). Please provide results from studies conducted to assess if endotoxin recovery is affected by the polysorbate-containing Vedolizumab drug product formulation. Undiluted drug product test samples should be spiked with endotoxin and satisfactory endotoxin recoveries should be demonstrated over time. The studies should be conducted in the same type of containers [redacted] (b) (4) [redacted] (b) (4)) in which the product and samples are held prior to endotoxin testing.

4) Regarding your Amendment 125476.25 response to Question 19 stating that the rabbit pyrogen test has not been performed in lieu of the results obtained for endotoxin testing by the LAL method, it is noted that the *July 2012 Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers* states that the requirement in 21CFR610.13(b) may be waived if an equivalent method is used. However, equivalence using the LAL assay has not been verified. In addition, the LAL test is not capable of detecting non-endotoxin pyrogens. Please perform the rabbit pyrogen test on three different drug product lots as per the requirements of USP <151>, *Pyrogen Test*, to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin.

5) Your Amendment 125476.30 response to Question 8 states that validation of (b) (4) stopper (b) (4) was conducted with a a (b) (4). This configuration differed from the (b) (4) stopper (b) (4) used for commercial manufacture (b) (4) Please justify why a (b) (4) rather than the (b) (4) commercial stopper (b) (4) was used for stopper (b) (4) validation.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
11/13/2013

From: Bugin, Kevin
To: Quinn, Karen (Karen.Quinn@takeda.com); Costello, Colleen (Colleen.Costello@takeda.com)
Cc: Bugin, Kevin
Subject: BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Quality - November 08, 2013
Date: Friday, November 08, 2013 11:02:37 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Quality information for your product and have the following requests for information. We request that you provide your response by November 14, COB.

A. There are concerns regarding the clonality of the vedolizumab production cell line. The estimated probability of clonality (b) (4) does not provide sufficient assurance that the master cell bank (MCB) is derived from a single progenitor cell. We note that there were (b) (4)

1. Provide any available additional data to support monoclonality of the MCB.

2. If sufficient additional data cannot be supplied at this time, propose additional testing or procedures to confirm the monoclonality of the MCB. For example, repeating a (b) (4) using a vial of the MCB and evaluating an appropriate number of clones by a sensitive method to evaluate the identity of the integration sites. This testing could be performed as part of a post-marketing commitment.

B. Given the concerns regarding the clonality of the vedolizumab cell line and the changes in the process for manufacturing a new working cell bank (WCB), the lists of testing requirements for qualification of the new WCB ((b) (4) and subsequent WCBs (Section 3.2.S.2.3, Tables 3-4 and 3-5) are not acceptable.

1. A WCB qualification protocol should be provided to the BLA. The protocol should identify all characterization assays used for qualification, and the acceptance criteria should be specific. Testing should be modified to include, for example, more comprehensive analyses of (b) (4) than are included as part of release testing.

2. The new WCB ((b) (4) should not be released for use until it is tested according to the modified protocol and meets the acceptance criteria.

3. All future WCBs should be qualified according to the same protocol until the monoclonality of the MCB is sufficiently demonstrated.

4. We recommend that the Control of Materials section (Section 3.2.S.2.3.3.2) be

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M. The DS and DP Post-approval Stability Protocol and Stability Commitment sections (3.2.S.7.2 and 3.2.P.8.2) should be revised to include a commitment to provide updated results from the ongoing stability studies and the annual commitment lots in the Annual Report.

N. [redacted] (b) (4) .

If you have any questions, please note that the quality review team is available for clarifications on November 12, 2013, between 1:00 and 6:00 PM for a brief 30 teleconference.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
11/08/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Clinical - November 08, 2013
Date:	Friday, November 08, 2013 11:02:19 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Clinical information for your product and have the following requests for information. We request that you provide your response by November 15, COB.

> In the 120-Day Safety update submitted to BLA 125476 and BLA 125507, there was 1 case reported of markedly elevated transaminases without associated signs/symptoms of liver failure. To facilitate our review of this case, we request that you provide additional details on this patient including the case report forms (Patient ID: C13006-42016-069).

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
11/08/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Quinn, Karen (Karen.Quinn@takeda.com); Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Carton/Container Labeling - November 05, 2013
Date:	Tuesday, November 05, 2013 10:00:04 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Carton and Container labeling for your product and have the following requests for information. We request that you provide your response and updated carton and container labeling by November 11, COB.

-

Information Request for Carton Container Label

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.]
   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>.

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*

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).

IV. Vial Cap and [redacted] (b) (4)
   a. Please comment on if there is any text on the [redacted] (b) (4) and cap overseal. A revised USP standard will go into effect on December 1, 2010. We refer you to the following address: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

*Recommended Format

Entyvio

vedolizumab

For Injection

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
11/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476/0
BLA 125507/0

MID-CYCLE COMMUNICATION

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Biologic License Applications (BLAs) submitted under section 351(a) of the Public Health Service Act for Entyvio (vedolizumab.

We also refer to the teleconference between representatives of your firm and the FDA on October 04, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 04, 2013, from 2:00 to 3:30 PM, ET

Application Number: BLA 125476/BLA 125507
Product Name: Entyvio (vedolizumab)
Indication: ulcerative colitis/Crohn's disease
Applicant Name: Takeda Pharmaceuticals U.S.A., Inc.

Meeting Chair: Anil Rajpal
Meeting Recorder: Kevin Bugin

FDA ATTENDEES:

Office of the Center Director
Rich Moscicki, M.D., Deputy Center Director of Operations

Office of Drug Evaluation III
Julie Beitz, MD, Director
Giuseppe Randazzo, BS, Regulatory Scientist

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, MD, Director
Joyce Korvick, MD, MPH, Deputy for Safety
Anil Rajpal, MD, MPH, Clinical Team Leader
Laurie Muldowney, MD, Clinical Reviewer
Klaus Gottleib, MD, MBA, RAC, Clinical Reviewer
Sushanta Chakder, PhD, Nonclinical Team Leader
Tamal Chakraborti, PhD, Nonclinical Reviewer
Kevin Bugin, MS, RAC, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Pharmacometrics
Nitin Mehrotra, PhD, Team Leader

Office of Biotechnology Products/Division of Monoclonal Antibodies
Rashmi Rawat, PhD, Team Leader
Qing (Joanna) Zhou, PhD, Reviewer

Office of Biotechnology Products/Biotechnology Assessment Branch
Patricia Hughes, PhD, Team Leader
Steve Fong, PhD, Reviewer, Drug Product

Reyes Candauchacon, PhD, Reviewer, Drug Substance

Office of Biostatistics/Division of Biometrics III
Freda Cooner, PhD, Acting Team Leader
Milton Fan, PhD, Reviewer

Office of Biostatistics/Division of Biometrics VII
John Yap, PhD, Reviewer

Office of Safety and Epidemiology/Division of Risk Management
George Neyarapally, PharmD, Reviewer

Office of Safety and Epidemiology/Division of Pharmacoviligance
Christian Cao, MD, Safety Evaluator

Office of Program & Strategic Analysis; Program Evaluation and Implementation Staff
Sharnell Ligon, Operations Research Analyst
Kimberly Taylor, Operations Research Analyst

Eastern Research Group
(b) (6) Independent Assessor of PDUFA V

APPLICANT ATTENDEES

Colleen Costello, PhD	Senior Director, Global Regulatory Affairs
Catherine, Milch, MD	Senior Director, Clinical Research
Asit Parikh, MD, PhD	Vice President, Gastroenterology and General Medicines R&D
Maria Rosario, PhD	Director, Clinical Pharmacology
Jesse Schick, MD	Medical Director, Medical Safety, Global Pharmacovigilance
Lesley Wise, PhD	Vice President, Global Risk Management and Pharmacoepidemiology
Karen Quinn, PhD	Senior Director, Regulatory Affairs - CMC
Norbert Schuelke, PhD	Director, Biologics Process Development
Veit Schmelmer, PhD	Senior Director, Drug Development Management
Irving Fox, MD, CM	Distinguished Medical Fellow, Clinical Development
Jing Xu, PhD	Director, Biostatistics
Serap Sankoh, PhD	Director, Biostatistics
Paul Hanson, PhD	Staff Engineer II
Chris Campbell	Associate Director, Cell Culture Process Development
Willow DiLuzio	Associate Director, Biologic Formulations

Eva Barbarics	Senior Scientist II, Analytical Development - Biologics
Meri Bloom	Global Regulatory Affairs
Vivek Kadambi, PhD	Vice President Drug Safety Evaluation
Melody Brown	Vice President, Global Regulatory Affairs
Bagyashree Sundaram	Director, Global Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

The following represent significant issues identified to date, which if left unresolved or not responded to will preclude approval.

Quality Microbiology of the Drug Product:

- Container closure integrity validation
- (b) (4) and (b) (4) validation
- Media fill simulation studies
- Endotoxin test method and test method validation
- Rabbit pyrogen test data
- Drug product shipping validation
- Validation of (b) (4) hour post-reconstitution storage period stated in label

Discussion:
Takeda requested clarification on the DP IR items.

3.0 INFORMATION REQUESTS

We note that there are outstanding information requests sent by the Agency pending a response by the Applicant. One information request related to clinical information sent on September 20, 2013, and two information requests related to the Qualify Microbiology of Drug Product (9/26) and Drug Substance sent on September 23, 2013.

Clinical/Statistics will be sending additional information requests related to the following in the near future:

- additional subgroup analyses
- additional sensitivity analyses
- summary statistics for Cohort 2
- tabulation of discontinuation (by time and reason)
- discrepancies within the documents submitted

- inconsistency in the treatment effect findings (for different endpoints and subgroups)

Discussion:
The Applicant requested clarification around discrepancies and inconsistencies. FDA clarified that the discrepancies were referring to the different numbers of Week 6 responders reported in different documents for Study C13006; and inconsistencies were regarding the inconsistent statistical significance observed for different efficacy endpoints and in different subgroups. FDA noted that those were exploratory findings and will be interpreted with caution. FDA noted that these will be issued within the next week.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The REMS proposal review is ongoing. The results of the AC meeting, including the discussion of the potential risk of PML and risk management approaches, may affect our final decision regarding the REMS.

Discussion:
The Applicant requested clarification about the timing of receiving feedback or meeting with the FDA regarding the REMS prior to the Late Cycle Meeting and the Advisory Committee. FDA notes that the earliest feedback could be provided with the FDA AC Background document.

5.0 ADVISORY COMMITTEE MEETING

A joint advisory committee meeting between the Gastrointestinal Advisory Committee and the Drug Safety and Risk Management Advisory Committee is scheduled for December 9, 2013, from 8:00 a.m. to 5:30 p.m. at the FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room (rm. 1503), Silver Spring, MD 20993-0002.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The Late Cycle Meeting (LCM) is tentatively scheduled for November 26, 2013, from 10:30 a.m. to 12:00 p.m., at FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 2 Conference Center, the Room 2045, Silver Spring, MD 20993-0002.

7.0 QUESTIONS FROM THE APPLICANT

(1) Please comment on whether we can expect to receive a REMS Notification Letter following the mid-cycle meeting.

FDA Response:
This determination has not yet been made.

Discussion:
Takeda requested clarification about this might occur. FDA noted that a final decision cannot be made until following the Advisory Committee meeting.

(2) Please comment on the status of FDAs review of the pediatric waiver and pediatric deferral requested in the BLA.

FDA Response:
The FDA's review is ongoing at this time and a determination regarding the acceptability of the requested pediatric waiver and pediatric deferral requested in the BLA has not yet been made.

Discussion:
Takeda requested additional information on timing. The FDA clarified that the earliest notification would be early 2014.

(3) Please comment on whether we should expect additional GMP inspections to be requested?

FDA Response:
No. We do not plan to conduct any additional GMP inspection.

(4) Please comment on the recommendation from the PAI inspection at (b) (4) to continue DNA testing, as this was identified as a BLA review issue. Are there any other (b) (4) PAI outcomes that may affect the review of the BLA?

FDA Response:
No.

Discussion:
FDA clarified that they will be shortly sending an Information Request related to the DNA testing.

(5) For the responses to the Requests for Information submitted to the BLA to date: Clinical, Statistics, Clinical Pharmacology, CMC and Nonclinical, Please confirm if the Sponsor's responses addressed the Agency's concern?

FDA Response:

The reviews of the Applicant's responses to the Agency's requests for information submitted to date are ongoing and we will provide additional comments at the Late Cycle Meeting (LCM).

(6) Following this Mid Cycle Communication, should the Sponsor expect to receive additional RFIs and/or Discipline Review Letters? Will all RFIs and/or Discipline Review letters be issued prior to the Late Cycle Meeting?

FDA Response:
We cannot confirm that the Applicant should expect to receive additional requests for information and/or Discipline Review letters, but it is possible that the Agency may have additional requests for information and/or Discipline Review letters as the reviews are ongoing at this time.

(7) Has FDA discussed the need for Post Marketing Commitments or Post Marketing Requirements? If so, will FDA comment on the scope and content of those discussions to date?

FDA Response:
Our reviews are ongoing and a determination has not yet been made regarding the need for Post Marketing Commitments or Post Marketing Requirements.

Discussion:
The Applicant requested clarification regarding the timing of communications regarding the post marketing commitments and post marketing requirements. The FDA clarified that comments regarding PMRs/PMCs would be communicated as they are developed, but final FDA comments on PMRs/PMCs would not be available until following the AC.

(8) Who from FDA will attend the Late Cycle Meeting? Please provide an overview of the format and content of the Late Cycle Meeting?

FDA Response:
The primary review team, in addition to consultants, signatory authorities and external contractors for PDUFA V will attend the LCM. A tentative attendee list will be provided in the LCM Briefing Package to be prepared by the FDA.

At the LCM, the FDA review team and the applicant discuss the status of the review late in the review cycle; the LCM is intended to enhance transparency and communication between the two parties. Potential topics of discussion include:

- **Application Deficiencies: Major deficiencies identified to date that may preclude approval if not resolved or that substantially affect labeling**
    - **The discussion should clearly delineate deficiencies with the potential to be resolved during the current review cycle from those not likely to be resolved during the current review cycle. However, the discussion should allow for the applicant to propose ways to address all deficiencies, including their proposed timeline for addressing them.**
    - **If there are no major deficiencies, minor issues may be discussed.**

- **Additional Sponsor Data: Additional data or analyses the applicant may wish to submit in response to FDA concerns/issues**
    - **FDA should consider and discuss the applicant's proposal without making a commitment or determination on whether the proposal addresses the deficiencies or is likely to be reviewed in the current review cycle.**

- **Advisory Committee (AC): AC meeting plans (if applicable)**
    - **Topics for discussion may include the review team's perspective on the major issues, potential questions to be posed to the committee, and coordination of FDA and applicant presentations to maximize the efficiency of the AC meeting.**

- **REMS/Risk Management: Current assessment of the need for REMS or other risk management actions**
    - **Any potential FDAAA safety post-marketing requirements (PMRs) should be discussed as well.**

- **Labeling: Important labeling issues**

- **Information Requests (IRs): Outstanding or new IRs**

- **Review Plans: FDA's plans/objectives for the remainder of the review**

- **Questions: Applicant questions**

Please see the CDER 21st Century Review Process Desk Reference Guide for additional information on the LCM, which is available at the following link: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf.

Discussion:
The Applicant asked for clarification about the timing of the LCM briefing package. The FDA clarified that this would be distributed 12 days prior to the LCM, November 14, 2013.

(9) Please confirm if the review remains "on-track" in accordance with the PDUFA V goals?

FDA Response:
Yes.

(10) Advisory Committee Planning Topics:

(a) Please confirm if the July 20, 2011 Closed Advisory Committee meeting will be referred to at the December 9, 2013 Advisory Committee meeting by FDA, in either briefing materials or presentation materials. If so, at what level of detail will it be referred? Please confirm if the Sponsor is permitted to discuss details of the July 20, 2011 Closed Advisory Committee meeting at the December 9, 2013 Advisory Committee Meeting, if the Sponsor so chooses.

FDA Response:
Although we will be referring to the July 20, 2011 Closed Advisory Committee meeting, we have not yet determined the level of detail to which it will be referred. You are permitted to discuss details of the July 20, 2011 Closed Advisory Committee meeting at the December 9, 2013 Advisory Committee Meeting, if you choose.

Discussion:
The FDA clarified that the Closed AC meeting would be referenced only to provide regulatory background regarding the position taken towards the safety of the product during the development stage.

(b) Please comment on what topics FDA plans to discuss with the Advisory Committee.

FDA Response:
The discussions will focus on the efficacy data for each of the proposed indications, safety data, and risk of PML (including discussion of requirements for REMS and postmarketing studies).

Discussion:
The FDA clarified that safety data presentations could be discussed further at the LCM

and specific plans cannot be discussed at this time.

(c) Please comment on the time allocated for the Sponsor presentation at the Advisory Committee Meeting.

FDA Response:
The agenda has not been finalized. However, we anticipate approximately 80 minutes for the sponsor presentation.

Discussion:
The Applicant requested clarification on the 80 minutes for presentation. The FDA noted that the 80 minutes does not include time for questions. The FDA would get back to the Applicant regarding the acceptability of the proposal once further work was done on the Agenda.

Post Meeting Comment:
After further internal discussion, the Agenda has been revised to allow 100 minutes of Sponsor presentation, plus 15 minutes for questions from the committee.

(d) Please comment on the format and/or the preliminary agenda for the Advisory Committee. Will the agenda mirror that used at the July 20, 2011 Closed Advisory Committee meeting?

FDA Response:
The agenda has not been finalized. However, we anticipate a full day meeting. It will not mirror the July 20, 2011 Closed Advisory Committee meeting because that meeting was primarily focused on the safety database; this meeting will also include discussion of other topics such as efficacy data for each of the proposed indications and more detailed discussion of the need for REMS and postmarketing studies. Furthermore, this AC will also have a one hour open public hearing.

(e) In the safety section of the Sponsors background materials, we plan on utilizing data from the 120-Day Safety Update (27 June 2013 data cut), as applicable. Please confirm if FDA agrees to harmonize on the safety data cut for AC Meeting materials.

FDA Response:
Please clarify when you intend to submit this data. Given the time constraints related to the expected date of submission of the 120-Day Safety Update and the date the FDA Background Document is due, the FDA may not have time to incorporate this into the FDA Background Document.

Discussion:
The Applicant clarified that the 120-Day Safety Update would be submitted on October

18, 2013. The Applicant and FDA agree that it would be best to have this data reviewed and presented at the AC.

(f) In an effort to facilitate communication of the different study populations for each indication, efficacy and safety, the Sponsor would like to clarify how the maintenance populations (efficacy and safety) for C13006 and C13007 will be represented in the sponsor's background materials and the slide presentation at the Advisory Committee. Please comment if FDA agrees to harmonize on the nomenclature for AC Meeting materials.

(i.) The evaluations of efficacy for UC and CD were conducted using the randomized, intent to treat (ITT) populations. The treatment groups for induction are VDZ and PBO and the treatment groups for maintenance include the following:

(1) Vedolizumab/Placebo (VDZ/PBO): Referring to patients who responded to treatment with 2 doses of VDZ during induction and were randomized to PBO during maintenance.

(2) Vedolizumab/vedolizumab Q8W (VDZ/VDZ Q8W): Referring to patients who responded to treatment with 2 doses of VDZ during induction and were randomized to VDZ Q8W during maintenance for up to 52 weeks.

(3) Vedolizumab/vedolizumab Q4W (VDZ/VDZ Q4W): Referring to patients who responded to treatment with 2 doses of VDZ during induction and were randomized to VDZ Q4W during maintenance for up to 52 weeks.

<u>FDA Response:</u>
Your proposal appears reasonable.

(ii.) The treatment groups for evaluation of induction safety are VDZ and PBO. The primary treatment groups for evaluation of safety across induction and maintenance include the following:

(1) Placebo/Placebo (PBO/PBO): Referring to patients who were treated with PBO during induction and PBO during maintenance for up to 52 weeks.

(2) Vedolizumab/Placebo (VDZ/PBO): Referring to patients who responded to treatment with 2 doses of VDZ during induction and were randomized to PBO during maintenance.

(3) Vedolizumab/vedolizumab (VDZ/VDZ; combined VDZ population): Referring to 2 groups of patients; one who responded to treatment with 2 doses of VDZ during induction and were randomized to either VDZ Q8W or VDZ Q4W during maintenance for up to 52 weeks and one who did not respond to induction treatment and were assigned to receive VDZ Q4W during maintenance for up to 52 weeks.

FDA Response:
Your proposal appears reasonable.

(g) To facilitate communication of the Crohn's Disease endpoints in Studies C13007 and C13011, enhanced clinical response will be denoted as "CDAI-100 Response" and clinical response will be denoted as "CDAI-70 Response" in the sponsor's Advisory Committee meeting materials. Please comment if FDA agrees to harmonize on the nomenclature for AC Meeting materials.

FDA Response:
Your proposal appears reasonable.

(h) The Sponsor is planning on presenting C13007 Induction primary endpoints in alignment with the final version of the protocol (i.e. post amendment 5/6) in which the Induction phase has 2 primary endpoints, clinical remission and enhanced clinical response. However, the Sponsor would like to be consistent with FDA's presentation regarding the primary endpoint(s) to minimize confusion to the Advisory Committee members. Based on discussions at the July 24th and 25th 2012 Type C meeting (Question 2), please confirm how FDA is planning on presenting the C13007 Induction primary endpoints.

FDA Response:
We will refer to the two C13007 Induction primary endpoints as "alternative primary endpoints." This is consistent with the following reference:

> **Offen W et al. "Multiple co-primary endpoints: medical and statistical solutions: a report from the multiple endpoints expert team of the Pharmaceutical Research and Manufacturers of America." Drug Information Journal 41, no. 1 (2007): 31-46.**
> **(available at: http://dij.sagepub.com/content/41/1/31.short)**

Additional Discussion:
The Applicant asked if the FDA can keep in mind the Applicant's deadline for an AC Background document and keep the Applicant informed of any issues that could impact the

discussions at the AC. The FDA will do its best to alert the Applicant to any issues that may impact the AC.

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/s/

KEVIN B BUGIN
10/30/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - OSI - October 30, 2013
Date:	Wednesday, October 30, 2013 9:16:57 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the Clinical and BIMO portions of your BLA and have the following requests for information. We request that you provide your response to this request by November 08, COB.

1. Provide both a narrative description and diagram for each protocol for the flow of data necessary to calculate the Crohn's Disease Activity Index (CDAI) or Mayo score used to determine the primary endpoint. This includes data from the office visit, patient diary, and other sources such as the clinical laboratory.
2. Describe the patient diary used for each study. For example, was the diary in a paper form or electronic and, if electronic, the nature of the data capture (e.g. IVRS or PDA)
3. State the entity responsible for calculation and analysis of the primary endpoint. Specifically, state whether a contract research organization (CRO) or you, the sponsor, performed the data manipulations and analysis. If performed by a CRO, provide the name of CRO.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
10/30/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com); Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Quality - October 30, 2013
Date:	Wednesday, October 30, 2013 9:14:09 AM

Hi Colleen and Karen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the quality portions of your BLA and have the following additional comments and requests for information. We request that you provide your response to this request by November 11, COB.

1. Regarding Process Characterization and Control Strategy for vedolizumab drug substance (DS) and drug product (DP) manufacturing process, provide information on the following items:
   a) The qualification data that adequately demonstrates that your small scale models are representative of the full scale process.

   b) The justification for the parameters selected for inclusion in your process characterization studies.

   c) The process characterization studies and/or risk assessments performed on the vedolizumab drug substance and drug product manufacturing processes to identify critical process parameters (CPP) and establish acceptable operating ranges for critical and non-critical process parameters.

2. Update section 3.2.S.2.2 with the osmolality ranges for the media used in (b) (4)

3. Update Table 5-1 in section 3.2.S.2.2 to include the (b) (4) ranges for the (b) (4) where applicable.

4. Your response to our IR-1 questions with regard certain process parameter and controls, stated that certain parameters are not included in 3.2.S.2.2 because they are controlled by the (b) (4)) is not acceptable. Update section 3.2.S.2.2 to include the following process parameters and in process controls with their (b) (4) and action limits respectively:

(b) (4)

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/s/

KEVIN B BUGIN
10/30/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com); Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Post Marketing Commitment Comments - Quality (Micro) - October 25, 2013
Date:	Friday, October 25, 2013 10:08:33 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

FDA Comment to Response to Information Request 4 submitted in amendment 0028
Submit a revisited risk assessment and validation protocol as a Prior Approval Supplement by March 30, 2013. Validation protocol should include which (b) (4) hold will be studied, number of replicates, and proposed action limits. Results from the validation study should be submitted to the Agency as in the following Annual Report and interim hold times based on manufacturing experience proposed in amendment 0021 should be used until then.

Please let us know if you agree to this commitment by October 31, 2013.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
10/25/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - Safety Statistics - October 23, 2013
Date:	Wednesday, October 23, 2013 2:10:28 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the 120 day safety update recently submitted. While we can find the analysis data and summaries of safety based on exposure data in days, we cannot locate this information based on the number of infusions. We request that you either identify the location of this data in the submission or provide it to us by October 31, COB.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
10/23/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com); Quinn, Karen (Karen.Quinn@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - Quality - October 16, 2013
Date:	Wednesday, October 16, 2013 8:16:50 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the quality portions of your applications and have the following requests for information. We request that you provide your response to this request by November 04, COB.

1. The concurrent validation protocols, [redacted] (b) (4), submitted to the BLA for reprocessing of the [redacted] (b) (4), respectively are missing page numbers 2, 4, and 6. Provide complete validation protocols and clarification on how the validation data will be reported to the Agency.

[redacted] (b) (4)

[redacted] (b) (4)

5. With regard to the potency assay used for release and stability testing of DS and DP, provide information on how the relative binding activity of MLN0002 is calculated. In addition, provide information on how the activity (i.e. EC50) of the reference standard is monitored over time in the assay.

6. Provide detailed protocol for the preparation of reference standard (RS) including, but not limited to, the formulation, concentration, quantity of vials prepared for current RS lot RS-010-04, amount of RS per vial, container and closure system. Provide a list of RS lots prepared to date including the information on the manufacturing process, date of

preparation and the size of each lot.

7. We note that several assays including assays for [redacted] (b) (4) are removed from the qualification of new RS lots. These tests need to be included in the qualification of new RS. Provide the acceptance criteria for each analytical method used to qualify a new vedolizumab RS.

8. Provide the Material Specification and the protocol for the requalification of existing RS. Include the information, but not limited to, retest period, requalification parameters and action in place in an event that the requalification of the existing RS fails.

9. Provide stability data for RS-010-04 and include stability data on freeze-thaw studies performed with RS-010-04.

10. Provide acceptance criteria for each analytical method used in the post-approval stability protocols.

[redacted] (b) (4)

13. Provide information on the storage conditions and stability monitoring of the HuT 78 and RPMI8866 cells.

14. Revise the drug substance and drug product release and stability specification for the [redacted] (b) (4) assay to control for all [redacted] (b) (4)

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
10/16/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin; Quinn, Karen (Karen.Quinn@takeda.com); Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending Information Request - Quality Micro
Date:	Wednesday, October 09, 2013 3:44:25 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the your response to Information Request submitted in amendment 0021 and have the following additional comments and requests for information. We request that you provide your response to this request by October 23, COB.

> Please submit revisited risk assessment and the protocol for the proposed (b) (4) validation studies; clarify which (b) (4) will be validated (b) (4) based on the new risk assessment. In addition, submit microbial quality (bioburden and endotoxin) results from (b) (4) used for the interim hold time proposal; include hold times and hold vessels.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
10/09/2013

From:	Bugin, Kevin
To:	Costello, Colleen (Colleen.Costello@takeda.com)
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical/Statistics - October 07, 2013
Date:	Monday, October 07, 2013 8:18:19 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the efficacy portions of your applications and have the following additional comments and requests for information. We request that you provide your response to this request by October 21, COB.

Statistics:

For ulcerative colitis study (C13006),

1. Please clarify the discrepancy in the numbers of vedolizumab patients who were Week 6 responders in the Induction Phase (Cohort 1) given in Table 18 of CSR and in the Open Label study (Cohort 2) given in Table 39.17.1.1, Response to Agency Question (106 in Cohort 1 and 231 in Cohort 2), and the number of patients who were randomized in the Maintenance Phase given in Figure 11 in CSR (373 randomized).

2. Please clarify the discrepancy in the number of patients completed the Induction Phase (Table 6) and the completers (observed case) population (Table 17) in CSR.

3. Please provide a summary of clinical remission at Week 6 for Cohort 2.

4. Please perform “observed-case” and per protocol analyses of clinical remission at Week 6 for the Induction Phase.

5. Please tabulate the numbers of patients who discontinued the study and discontinued due to lack of efficacy by treatment group and by week in the Maintenance Phase.

6. Please perform ”observed-cases” analysis of changes from baseline in partial Mayo score, complete Mayo score, endoscopy sub-score, rectal bleeding sub-score, stool frequency sub-score and PGA sub-score by study visits.

For Crohn's disease study (C13007)

1. Please perform analysis on clinical response at Week 6 for the Induction Study ITT Population and provide a summary of clinical response at Week 6 for the Cohort 2 population.

2. Please tabulate the numbers of patients who discontinued the study and discontinued due to lack of efficacy by treatment group and by week in the Maintenance Phase.

3. Perform a subgroup analysis for enhanced clinical response at Week 6 for the Induction Study ITT Population.

4. Please provide a reasonable explanation for the observation that the treatment difference achieved statistical significance for clinical remission at Week 6, but it failed to achieve statistical significance for enhanced clinical response at Week 6 for the Induction Study ITT Population.

5. Please provide reasonable explanation for the observation that there was inconsistency in the treatment difference of clinical remission at Week 6 by baseline CDAI ≤ 330 vs. CDAI> 330 (15.3% for CDAI ≤330 and -1.1% for CDAI >330).

6. Please provide a summary of proportions of patients who were observed in clinical remission and enhanced clinical response, separately, at all assessment time points from Week 6 to Week 52 with no imputation.

<u>Clinical</u>

The statistical reviewers had the following request for information: "4. Please provide reasonable explanation for the observation that the treatment difference achieved statistical significance for clinical remission at Week 6, but it failed to achieve statistical significance for enhanced clinical response at Week 6 for the Induction Study ITT Population." (Induction phase C13007)

The clinical reviewer suggests a possible approach:

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

analysis (p.138 Clinical Study Report C13007 Figure 6).

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
10/07/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - CMC (Micro) - September 26, 2013
Date:	Thursday, September 26, 2013 12:34:45 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the CMC portions of your applications and have the following additional comments and requests for information. We request that you provide your response to this request by October 15, COB.

1) Table 1-1 of Module 3.2.P.7 states that the manufacturer for the 5 mL Vedolizumab vials is (b) (4) As the quality and characteristics of vials provided by different vendors may vary, you should restrict the vendor to (b) (4) unless you can provide a justification that vials sourced from a different company are equivalent. For use of an alternate vendor the company should be specified.
2) The procedures, acceptance criteria and data for container-closure integrity (CCI) validation were not provided in the BLA. Please submit. In your response include:
   a) The CCI test method and acceptance criteria.
   b) The number of containers tested.
   c) The vacuum and pressure parameters, the time of challenge, and descriptions for positive and negative controls if the microbial or dye ingress methods are utilized.
   d) The detectable leak diameter for positive controls with known defects.
   e) The production parameter limits for crimper pressure, crimper height, and crimper rotational speed, and data demonstrating that integrity is maintained at the minimum and maximum allowable (worst case) crimper parameter limits.

3) Submit the room locations and room classifications for the following:

(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
09/26/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - CMC (Micro) - September 23, 2013
Date:	Monday, September 23, 2013 9:20:33 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the CMC portions of your applications, your response to our earlier information request and have the following additional comments and requests for information. We request that you provide your response to this request by October 04, COB.

FDA Comment to Response to Information Request 1.b (sequence 0009)

Alert limits for microbial quality (bioburden and endotoxin) should be established for all (b) (4) Alert limits should be based on historical data. Please submit (b) (4) alert limits for microbial quality.

FDA Comment to Response to Information Request 1.c (sequence 0009)

Endotoxin action limit for (b) (4) should be consistent with (b) (4) action limit for (b) (4) Please adjust endotoxin action limits for (b) (4)

FDA Comment to Response to Information Request 4 (sequence 0009)

Risk assessment RA-CA-003 is inadequate to support (b) (4) hold times because:

1. two of the elements of the risk assessments (historical bioburden and endotoxin data and historical frequency of extended hold) are not representative of worst-case conditions,
2. the weight of the other elements in the risk assessment (equipment and process handling; growth promotion; and temperature) is not supported by data

(b) (4)

Maximum (b) (4) hold times should be validated (b) (4) for microbial quality (bioburden and endotoxin). Validation should include three successful validation runs at manufacturing scale. Bioburden and endotoxin levels before and after maximum allowable hold time should be monitored and bioburden and endotoxin limits provided.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
09/23/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical - September 20, 2013
Date:	Friday, September 20, 2013 11:13:44 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical portions of your applications and have the following requests for information. We request that you provide your response to this request by October 04, COB.

1. Study C13006: Provide a sensitivity analysis on Completers (Observed Case) for the Primary Maintenance Study endpoint of clinical remission, where the Completers population consists of all Maintenance Study ITT patients designated as responders through IVRS in induction who received any amount of blinded study drug during the Maintenance Phase and have a Week 6 and Week 52 assessment for the endpoint under consideration (complete Mayo score).

2. C13006: Provide the proportion of patients with an endoscopy subscore of zero at Week 6 and Week 52 by treatment arm in the observed case analysis for combined induction cohort and by induction cohort.

3. C13006: Provide the proportion of patients in Clinical Remission at Week 6 by Maintenance Study treatment arm in the observed case analysis for combined induction cohort and by induction cohort.

4. C13006: Perform a subgroup analysis (based on prior anti-TNF failure) for clinical remission at Week 52, where anti-TNF failure is based on either inadequate response or loss of response.

If you have any questions, please do not hesitate to contact me

Regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
09/20/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical Pharmacology - September 19, 2013
Date:	Thursday, September 19, 2013 11:13:30 AM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical portions of your applications and have the following requests for information. We request that you provide your response to this request by September 25, COB.

> Based on your analysis of confounding factors for exposure response (Population PK Efficacy Report 2013), you have made a case that there is an exposure-response relationship for the phase 3 Ulcerative Colitis (UC) data for the induction phase after adjusting for all possible confounding factors. We have confirmed that based on our internal analysis utilizing only the ITT population.
>
> However, this finding is not supported by phase 2 data (study c13002 and M200-022) where no dose-response relationship is observed for the induction phase within the dose range of 0.5 to 10 mg/kg. It is apparent that the dose studied in the phase 3 trial (300 mg) falls in the range between 2 and 6 mg/kg on a body weight basis. The PK variability from the phase 2 trials is not suggestive that there is significant overlap between the PK exposures at these studies doses.
>
> Provide rational or evidence that can explain this discrepancy between the phase 2 and phase 3 data in UC patient population.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
09/19/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476/125507 Entyvio (vedolizumab) - Pending BLA Information Request - Nonclinical - September 16, 2013
Date:	Monday, September 16, 2013 8:53:51 PM

Hi Colleen,

Please refer to your Biologics License Applications (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the nonclinical portions of your applications and have the following requests for information. We request that you provide your response to this request as soon as possible.

Please provide either the location of, or resubmit, the original report of the following toxicology study as soon as possible. We are only able to find the amended report (Amendment No. 2) submitted in Section 4.2.3.2.

KLA00290 - A 26-Week Toxicity Study of MLN0002 Administered by Intravenous Infusion to Cynomolgus Monkeys, with a 12-Week Recovery Period

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
09/16/2013

From: Bugin, Kevin
To: "Costello, Colleen"
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical - September 03, 2013
Date: Tuesday, September 03, 2013 3:52:09 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical portions of your application and have the following requests for information. We request that you provide your response to this request by September 09, 2013, close of business.

1. Provide a summary of JCV DNA testing results for all Phase 3 studies. This can be provided in a table similar to that shown below. Please also specify if any patients with a positive JCV DNA test had positive RAMP algorithm results.

	C13006		C13007		C13011		C13008	TOTAL	
	PLA N =	VDZ N =	PLA N=	VDZ N =	PLA N =	VDZ N =	VDZ N =	PLA N =	VDZ N =
Subjects tested									
Transiently positive, n(%)									
Persistently positive[a], n (%)									
Negative, n (%)									
Specimens tested									
Positive, n (%)									
Negative, n (%)									

[a] persistently positive is defined as detectable viremia on 2 separate occasions over a 180-day period and separated in time by at least 30 days

2. Provide an updated table summarizing the number of vedolizumab infusions by prior and concomitant immunosuppressant use that includes studies C13002 and C13004 and that matches the exposure numbers for overall exposure.

Category	Number of Vedolizumab Infusions[a,b]				
	≥ 6 N = 2136	≥ 12 N = 1436	≥ 18 N = 1136	≥ 24 N = 869	≥ 36 N = 385
Prior Immunosuppressant Use					
Yes	1735 (81)	1155 (80)	900 (79)	678 (78)	296 (77)
No	401 (19)	281 (20)	236 (21)	191 (22)	89 (23)
Concomitant Immunosuppressant Use[c]					
Yes	596 (28)	440 (31)	349 (31)	261 (30)	103 (27)
No	1540 (72)	996 (69)	787 (69)	608 (70)	282 (73)

[a] Includes only studies C13006, 13007, 13008, and 13011; because 13002 and 13004 are not included, the exposure numbers do not match the overall exposure numbers

[b] Patients had a minimum of 4 weeks follow-up after the last infusion

[c] All US patients are classified as no concomitant immunosuppressant use

3. For patients outside the US enrolled in C13006, C13007, C13008, and C13011, provide a summary table of concomitant immunosuppressant use by months of concomitant exposure.

This can be provided in a table similar to that shown below:

Duration	Ulcerative Colitis N =	Crohn's Disease N =	Total N =
At least 1 dose, n (%)	xx (%)	xx (%)	xx (%)
Months of Exposure to concomitant immunosuppressants			
≥ 3	xx (%)	xx (%)	xx (%)
≥ 6	xx (%)	xx (%)	xx (%)
≥ 12	xx (%)	xx (%)	xx (%)
≥ 18	xx (%)	xx (%)	xx (%)
≥ 24	xx (%)	xx (%)	xx (%)
≥ 36	xx (%)	xx (%)	xx (%)
≥ 48	xx (%)	xx (%)	xx (%)

4. Please provide a table which summarizes the study and treatment arm from which rollover patients to Study C13008 originated.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
09/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476
BLA 125507

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Biologics License Applications (BLAs), dated June 20, 2013, received June 20, 2013, submitted under section 351(a) of the Public Health Service Act for Entyvio, (vedolizumab).

We also refer to our filing notification letters dated August 19, 2013.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The section heading in Highlights for [redacted] (b) (4) is an optional section. If this section does not contain actionable information, please remove.

2. In the "Indications and Usage" Highlights section, you should revise the text such that only the name of the class is used, i.e. "integrin receptor antagonist."

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by September 16, 2013. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the request is denied.

If you have any questions, call Kevin Bugin, Senior Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Richard W. Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/30/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical Pharmacology - August 23, 2013
Date:	Friday, August 23, 2013 8:35:07 AM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical pharmacology portions of your application and have the following requests for information. We request that you provide your response to this request by September 09, 2013, close of business.

> We note that your analysis of immunogenicity impact on PK was based on comparisons between subjects with positive antidrug antibody (ADA) status and subjects with negative ADA status. Because there are a small number of ADA positive subjects in your Phase 3 trials partially due to the drug interference in your ADA assay, additional analyses are necessary. For instance, the impact of ADA on PK can be evaluated based on intra-subject comparison of vedolizumab concentrations before and after ADA development. We request the following information to facilitate our independent assessment of the impact of immunogenicity on PK and efficacy of your product.
>
> Provide an analysis dataset (as a SAS transport file) containing data from individual subjects who were identified to be ADA+ at one or more time points after vedolizumab administration. The requested dataset is to include subjects with persistently positive ADA and subjects with transiently positive ADA in all Phase 3 trials (Studies C13006, C13007 and C13011). Some recommended data variables to be included are shown in the attached mockup table.
>
> Provide individual concentration-time profile plots (linear scale and one plot per individual subject) for subjects with transiently or persistently ADA+ status. In each plot, overlay the ADA status-time profile. For graphical illustration, assign an arbitrary number of 10 to indicate ADA+, 1 for ADA- and 4 for NA.

If you are unable to meet the above referenced deadline, or have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

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301-796-2302

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/s/

KEVIN B BUGIN
08/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Takeda Pharmaceuticals U.S.A., Inc.
40 Landsdowne Street
Cambridge, MA 02139

Attention: Colleen Costello, Ph.D.
Sr. Director, Regulatory Affairs

Dear Dr. Costello:

Please refer to your Biologics License Application (BLA) dated and received June 20, 2013, submitted under section 351 of the Public Health Service Act, for Vedolizumab, for Injection 300 mg per vial.

We also refer to your July 25, 2013, correspondence, received July 25, 2013, requesting review of your proposed proprietary name, Entyvio. We have completed our review of the proposed proprietary name, Entyvio, and have concluded that it is acceptable.

The proposed proprietary name, Entyvio will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 25, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kevin Bugin at (301) 796-2302.

.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
08/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476

FILING NOTIFICATION

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Biologics License Application (BLA), dated June 20, 2013, received June 20, 2013, submitted under section 351(a) of the Public Health Service Act for Entyvio, (vedolizumab) 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 (TNFα) antagonist.

We also refer to your amendments dated August 08, 2013, July 31, 2013, July 25, 2013, July 24, 2013, July 08, 2013, July 03, 2013, April 08, 2013, and March 27, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is February 18, 2013.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 20, 2013. In addition, the planned date for our internal mid-cycle review meeting is

September 26, 2013. We are currently planning to hold an advisory committee meeting to discuss this application.

While conducting our filing review, we have identified potential review issues and will be communicating them to you on or before September 02, 2013.

If you have any questions, call Kevin Bugin, Senior Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
08/19/2013
Signing for Donna Griebel.

From: Bugin, Kevin
To: "Costello, Colleen"
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical/Statistics - August 19, 2013
Date: Monday, August 19, 2013 9:01:51 AM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical portions of your application and have the following requests for information. We request that you provide your response to this request by September 09, 2013, close of business.

CD and UC Phase 3 Trials:

1. Studies C13006, C13007, and C13011: Provide a high-level description of the histological assessments that were obtained in the studies. Specifically, provide the proportion of patients by study that had standardized histological assessments of the mucosa (i.e., histological assessments using a particular scoring system) at one or more timepoints as shown in the table below. Specify the particular scoring systems that were used, and provide separately for each scoring system the proportion of patients by study that had standardized histological assessments using that scoring system at one or more timepoints as shown in the table below.

Table 1. High-Level Description of Standardized Histological Assessments Obtained (Proportion of Patients) (Studies C13006, C13007, and C13011)

Timepoints	C13006	C13007	C13011
Standardized Histological Assessments			
Baseline	n/N (%)	n/N (%)	n/N (%)
End of Induction	n/N (%)	n/N (%)	n/N (%)
End of Maintenance	n/N (%)	n/N (%)	--
Baseline and End of Induction	n/N (%)	n/N (%)	n/N (%)
Baseline, End of Induction, and End of Maintenance	n/N (%)	n/N (%)	--
End of Induction and End of Maintenance	n/N (%)	n/N (%)	--
Baseline and End of Maintenance	n/N (%)	n/N (%)	--
Histological Assessments using Scoring System A			
Baseline	n/N (%)	n/N (%)	n/N (%)
End of Induction	n/N (%)	n/N (%)	n/N (%)
End of Maintenance	n/N (%)	n/N (%)	--
Baseline and End of Induction	n/N (%)	n/N (%)	n/N (%)
Baseline, End of Induction, and End of Maintenance	n/N (%)	n/N (%)	--
End of Induction and End of Maintenance	n/N (%)	n/N (%)	--

Baseline and End of Maintenance	n/N (%)	n/N (%)	--
Histological Assessments using Scoring System B			
Baseline	n/N (%)	n/N (%)	n/N (%)
End of Induction	n/N (%)	n/N (%)	n/N (%)
End of Maintenance	n/N (%)	n/N (%)	--
Baseline and End of Induction	n/N (%)	n/N (%)	n/N (%)
Baseline, End of Induction, and End of Maintenance	n/N (%)	n/N (%)	--
End of Induction and End of Maintenance	n/N (%)	n/N (%)	--
Baseline and End of Maintenance	n/N (%)	n/N (%)	--
etc.			

CD Phase 3 Trials:

2. Studies C13007 and C13011: Provide as an exploratory analysis by treatment group the proportion of patients in clinical remission at Week 6 (Study C13007), the proportion of patients in clinical remission at Week 52 (Study C13007), the proportion of patients in clinical remission at Week 6 in the TNFα antagonist failure subpopulation (Study C13011), and the proportion of patients in clinical remission at Week 6 in the entire study population (Study C13011) based on the following alternate definition of clinical remission (using daily patient diary data collected for calculation of the CDAI; patients must meet both criteria below):
   - Total number of liquid/very soft stools of ≤ 10 in the relevant week; and
   - Abdominal pain rated as 0 or 1 for each day in the relevant week.

3. Studies C13007 and C13011: Provide information on the collection of data for calculation of the CDAI including the following:
   - the exact questions asked of patients in the diary, and
   - the instructions given to patients on completion of the diary

4. Studies C13007 and C13011: Perform exploratory analyses of the primary endpoint and secondary endpoints without imputation for Studies C13007 and C13011.

5. Studies C13007 and C13011: For addressing the issue of missing data, perform the following sensitivity analyses for the primary endpoint and secondary endpoints for Studies C13007 and C13011:
   - Observed case: exclude subjects from the analysis at a specific time point if the patients have insufficient data at that time point.
   - Complete case: exclude subjects from the analysis at all time points if they have insufficient data at any of the time points of analysis.
   - Worst case: (1) subjects with missing observations at any of the time points of analysis are

assumed to be non-responders; (2) subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be responders, and subjects receiving treatment with missing observations at any of the time points of analysis are assumed to be non-responders.

- LOCF analysis
- Multiple imputation

6. Study C13007: Perform subgroup analyses (based on prior anti-TNF failure) for clinical remission and "enhanced clinical response" at Week 6 in Study C13007 by Cohort. For these analyses, anti-TNF failure should be based on either inadequate response or loss of response.

7. Study C13011: Perform subgroup analyses (based on prior anti-TNF failure) for clinical remission at Week 6 in Study C13011. For these analyses, anti-TNF failure should be based on either inadequate response or loss of response.

8. Study C13007: Provide a summary of the concomitant medications for IBD used at any time during the Induction Phase by patients in Cohort 2 for Study C13007.

9. Study C13007: Provide a summary of results for clinical remission and "enhanced clinical response" at Week 6 for Cohort 2 in Study C13007.

10. Study C13007: Provide analyses of the primary and secondary endpoints for Study C13007 prior to Amendment 5/6 and after Amendment 5/6.

11. Study C13007: Provide an explanation for why the results from Cohort 1 are not similar to those from Cohort 2 for the primary and secondary endpoints in the Maintenance Phase for Study 13007.

UC Phase 3 Trials:

12. Study C13006: Perform the following exploratory analyses of the primary endpoint and secondary endpoints:

    a. without imputation;

    b. subjects with less than 3 days of diary data within 7 days prior to a study visit should be classified as non-responders.

13. Study C13006: For addressing the issue of missing data, perform the following sensitivity analyses for the primary endpoint and secondary endpoints for Study C13006:

- Observed case: exclude subjects from the analysis at a specific time point if the patients have insufficient data at that time point.
- Complete case: exclude subjects from the analysis at all time points if they have insufficient data at any of the time points of analysis.
- Worst case: (1) subjects with missing observations at any of the time points of analysis are assumed to be non-responders; (2) subjects receiving placebo with missing observations at any of the time points of analysis are assumed to be responders, and subjects receiving treatment with missing observations at any of the time points of analysis are assumed to be non-responders.
- LOCF analysis
- Multiple imputation

14. Study C13006: For the Maintenance Phase in Study 13006, perform a Bonferroni-based gatekeeping procedure to test all endpoints in the primary endpoint family and proceed to the secondary family of endpoints only if there has been statistical success in the primary family. This analysis will be considered exploratory. However, when it is used as a pre-specified gatekeeping strategy to test the primary family endpoints, the Bonferroni method has an important property of preserving some alpha for testing the secondary endpoint family when at least one of the endpoints in the primary family is statistically significant. The endpoint-specific alpha from each test that successfully rejects the null hypothesis is summed and becomes the alpha available to the secondary endpoint family.

15. Study C13006: Perform subgroup analyses (based on prior anti-TNF failure) for clinical response at Week 6 in Study C13006 by Cohort. For these analyses, anti-TNF failure should be based on either inadequate response or loss of response.

16. Study C13006: Provide a summary of the concomitant medications for IBD used at any time during the Induction Phase by patients in Cohort 2.

17. Study C13006: Provide a summary of clinical response at Week 6 for the Cohort 2 population.

18. Study C13006: Provide an explanation why results for clinical remission at Week 6 are different from those using the more stringent definition of clinical remission (i.e., complete Mayo score of ≤ 2 points and no individual subscore > 1 point

where rectal bleeding subscore = 0 and endoscopy subscore = 0; see Page 20 of the Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA)). The number of patients achieving clinical remission at Week 6 changed from 8 to 4 in the placebo arm and from 38 to 10 in vedolizumab arm (see Table 19 of the C13006 Study Report and Table 3-6 of the Ulcerative Colitis Supplemental Efficacy Analysis Report (C13006 FESA)).

19. Study C13006: Provide exploratory analyses of clinical remission based on the following four endpoint definitions for Study C13006:

    a. Endoscopy subscore = 0, Rectal Bleeding subscore = 0, and Stool Frequency subscore decreases or no change from Baseline (all assessed at Week 6)
    b. Endoscopy subscore ≤ 1, Rectal Bleeding subscore = 0, and Stool frequency subscore = 0 (all assessed at Week 6)
    c. Endoscopy subscore ≤ 1, Rectal Bleeding subscore = 0, and Stool frequency subscore ≤ 1 (all assessed at Week 6)
    d. Endoscopy subscore ≤ 1, Rectal Bleeding subscore = 0, Stool Frequency subscore decreases or no change from Baseline, and Total score ≤ 1 (all assessed at Week 6)

Other:

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

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

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

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
08/19/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical - August 08, 2013
Date:	Thursday, August 08, 2013 7:11:18 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical portions of your application and have the following requests for information. We request that you provide your response to this request by August 26, 2013, close of business.

1. For Studies C13006 and C13007, please provide updated AE, LB, and CM datasets, which include the EPOCH variable. The inclusion of an EPOCH variable within these domains will significantly aid our review of these studies. This variable enables the review team to easily determine the phase of the trial where an observation or intervention occurred. The separation between the phases for these studies is particularly important since the domains include data from the Induction and Maintenance Phases together. While the EPOCH variable is not yet required, the CDER Common Data Standards Issues Document outlines the importance of EPOCH as an Expected or Permissible variable. For the purposes of SDTM submissions to CDER, all Permissible and Expected variables for which data were collected or for which derivations are possible should be submitted.

2. Studies C13006 and C13007:

   a. In each of the trials, one of your secondary endpoints for the maintenance phase (corticosteroid-free remission) appears to be defined as the proportion of patients that begin corticosteroid taper at Week 6 and achieve clinical remission without receiving corticosteroids at the end of the maintenance period (Week 52). Provide for each trial, by treatment arm, the following:
      - Proportion of subjects who are corticosteroid-free at Week 52 regardless of clinical remission status at Week 52.
      - Descriptive statistics for the baseline steroid dose (present overall results and results separated by status of corticosteroid-free remission secondary endpoint).
      - Descriptive statistics for the number of days that patients did not receive corticosteroids during the maintenance phase (present overall results and results separated by status of corticosteroid-free remission secondary endpoint).

   b. In each of the trials, you have included two exploratory endpoints for the maintenance phase that specify the duration a patient must be corticosteroid-free as 90 days and as 180 days. Provide for each trial by treatment arm, the following:
      - Proportion of subjects who have been corticosteroid-free for 90 days regardless of clinical remission status at Week 52.

- Proportion of subjects who have been corticosteroid-free for 180 days regardless of clinical remission status at Week 52.

3. Studies C13006 and C13007: For each trial, provide subgroup analyses for the primary and secondary endpoints of both the induction and maintenance studies based on whether patients met the criteria outlined in Amendment 2 (28 Oct 2008) (US-specific amendment) to each protocol. Specifically, provide summary results for the primary and secondary endpoints (for induction and maintenance) by treatment group for each of the two trials in the following two categories:
    a. Met US protocol criteria [i.e., must have previously demonstrated an inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists (instead of the less stringent requirement of inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists or steroids) and must not have received concomitant immunomodulators beyond Week 6].
    b. Did not meet US protocol criteria.

    Note that if patients were enrolled outside the US but met the US protocol criteria described above, they should be included in category (a) above.

4. Study C13011: Provide subgroup analyses for the primary and secondary endpoints based on whether patients met the US versus Ex-US criteria as described on Page 31 of the protocol. Specifically, provide summary results for the primary and secondary endpoints by treatment group in the following two categories:
    a. Met US protocol criteria [i.e., must have previously demonstrated an inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists (instead of the less stringent requirement of inadequate response to, loss of response to, or intolerance of immunomodulators or TNFα antagonists or steroids)].
    b. Did not meet US protocol criteria.

    Note that if patients were enrolled outside the US but met the US protocol criteria described above, they should be included in category (a) above.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
08/08/2013

From: Bugin, Kevin
To: "Costello, Colleen"
Cc: Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending BLA Information Request - Clinical - August 02, 2013
Date: Friday, August 02, 2013 5:15:11 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical and safety portions of your application and have the following requests for information. We request that you provide your response to this request by August 09, 2013, close of business.

1. Provide an explanation for the difference between the number of patients with ≥ 24 months vedolizumab exposure (835) and the number of patients with ≥ 24 vedolizumab infusions (903), for example:

   The table below shows the number of patients per study who received at least 24 VDZ infusions (column 2). Among these patients, some in Studies C13006, C13007, and C13011 had <24 months of VDZ exposure (column 3). Clarify why, in these studies (and in general), there is discordance between the numbers of infusions and months of VDZ exposure.

Study	#Patients with ≥24 infusions	#Patients with <24 months exposure
C13002	21	0
C13004	13	0
C13006	399	25
C13007	441	35
C13011	29	25
Total	903	85

2. The dataset cut-off date for Study C13008 is July 16, 2012. Submit updated datasets for Study C13008 with a cut-off date that matches the ISS (i.e. March 14, 2013).

If you have any questions on this request, please do not hesitate to contact me.

Kind regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER

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KEVIN B BUGIN
08/02/2013

From: Bugin, Kevin
To: Quinn, Karen (Karen.Quinn@MPI.com)
Cc: "Costello, Colleen"; Bugin, Kevin
Subject: BLA 125476 Entyvio (vedolizumab) - Pending BLA Information Request - Quality - July 31, 2013
Date: Wednesday, July 31, 2013 7:51:13 AM

Hi Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the quality portions of your application and have the following requests for information. We request that you provide your response to this request by August 21, 2013, close of business.

1. Description of the Manufacturing Process and Process Controls

   a. Provide a diagram of the manufacturing process and indicate for each step at which point the following events take place:

(b) (4)

   b. Submit microbial quality Action and Alert limits for al (b) (4) steps.

   c. Submit microbial quality sample size.

   d. Submit microbial quality limits of (b) (4)

   e. Indicate if the target temperature during shipping is (b) (4)

(b) (4)

3. Process Validation Batches

(b) (4)

(b) (4)

4. Validation of Maximum Hold Times – (b) (4) Holds

Indicate when microbial quality results from the validation of maximum hold times of (b) (4) will be submitted to the Agency.

5. Validation of Maximum Hold Times – (b) (4)

Submit microbial quality specifications of (b) (4)

6. Shipping Validation

(b) (4)

7. Analytical Procedures

Describe the bioburden and endotoxin methods

8. Validation of Analytical Procedures

   a. Provide summary and validation report of bioburden and bacterial endotoxin method suitability tests.
   b. Indicate if method suitability tests for bioburden and endotoxin have been conducted for (b) (4) samples and submit summary report and results.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
07/31/2013

From:	Bugin, Kevin
To:	Quinn, Karen (Karen.Quinn@MPI.com)
Cc:	"Costello, Colleen"; Bugin, Kevin
Subject:	BLA 125476 vedolizumab - Pending BLA Information Request - Quality - July 23, 2013
Date:	Tuesday, July 23, 2013 1:59:12 PM

Hi Karen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the quality portions of your application and have the following requests for information. We request that you provide your response to this request by August 23, 2013, close of business.

(b) (4)

[redacted]

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KEVIN B BUGIN
07/23/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin (kevin.bugin@fda.hhs.gov)
Subject:	BLA 125476 vedolizumab - Pending BLA Information Request - Clinical Pharmacology - July 22, 2013
Date:	Monday, July 22, 2013 2:47:00 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical pharmacology portions of your application and have the following requests for information.

- Submit each of the input files used in the NONMEM output codes for the base and final PK and PD models found in your Pop PK PD Report, titled: "Population Pharmacokinetic and Pharmacodynamic Modeling of Vedolizumab in Subjects with Crohn's Disease and Ulcerative Colitis for Studies C13002, C13006, C13007, C13009, and C13011". If they have already been submitted or renamed, please indicate the correct name and location of these files. These include "mcm4hip_dat03.csv" and "tran01.csv". If you have submitted the files described in "revieweraid.pdf", please describe where those can be found. This file was found in the following location: <STN125476\0002\m5\datasets\metrum-population-pk-pd\analysis\legacy\datasets>.

- Please submit the Microsoft Word file format of the pdf file entitled "clinical pharmacology summary" under eCTD session 1.11.3.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

_____
Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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KEVIN B BUGIN
07/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476

BLA ACKNOWLEDGEMENT

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Proprietary Name To Be Determined (vedolizumab)

Date of Application: 20 JUNE 2013

Date of Receipt: 20 JUNE 2013

Our Secondary Tracking Number (STN): BLA 125476

Proposed Use: 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 (TNFα) 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 (TNFα) antagonist.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}
Kevin Bugin, M.S., R.A.C.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
06/27/2013

From: Bugin, Kevin
To: "Costello, Colleen"
Cc: Bugin, Kevin
Subject: BLA 125476 vedolizumab - Pending BLA Information Request - Clinical - June 27, 2013
Date: Thursday, June 27, 2013 4:49:58 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted on June 20, 2013, under section 351(a) of the Public Health Service Act for vedolizumab.

We are reviewing the clinical portions of your application and have the following requests for information. We request you provide a response to these requests for information by July 08, 2013.

1. For each of your Phase 3 studies (i.e., Studies C13006, C13007, and C13011) provide for each phase (induction and maintenance) a table that shows the proportion of patients (ITT Population) that met the primary endpoint by study site (in descending order of numbers of patients at each study site) and by treatment group; summarize results for U.S. sites separately from results for international sites. The tables should look substantially like the following:

Table 1. Study C13006 Induction Phase (ITT Population): Proportion of Patients that Met Primary Endpoint by Study Site

Study Site		Proportion of Patients that Met the Primary Endpoint	
Site #	Number of Pts at Site	Vedolizumab	Placebo
U.S. Sites			
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
.	.	.	.
.	.	.	.
.	.	.	.
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
International Sites			
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
.	.	.	.
.	.	.	.
.	.	.	.
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)

Table 2. Study C13006 Maintenance Phase (ITT Population): Proportion of Patients that Met Primary Endpoint by Study Site

Study Site		Proportion of Patients that Met the Primary Endpoint		
Site #	Number of Pts at Site	Vedolizumab Q 8 weeks	Vedolizumab Q 4 weeks	Placebo
U.S. Sites				
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
International Sites				
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)

Table 3. Study C13007 Induction Phase (ITT Population): Proportion of Patients that Met Primary Endpoint by Study Site

Study Site		Proportion of Patients that Met the Primary Endpoint	
Site #	Number of Pts at Site	Vedolizumab	Placebo
U.S. Sites			
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
.	.	.	.
.	.	.	.
.	.	.	.
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
International Sites			
…	x	n/N (%)	n/N (%)

…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
.	.	.	.
.	.	.	.
.	.	.	.
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)

Table 4. Study C13007 Maintenance Phase (ITT Population): Proportion of Patients that Met Primary Endpoint by Study Site

Study Site		Proportion of Patients that Met the Primary Endpoint		
Site #	Number of Pts at Site	Vedolizumab Q 8 weeks	Vedolizumab Q 4 weeks	Placebo
U.S. Sites				
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
International Sites				
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
…	x	n/N (%)	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)	n/N (%)

Table 5. Study C13011 Induction Phase (ITT Population): Proportion of Patients that Met Primary Endpoint by Study Site

Study Site		Proportion of Patients that Met the Primary Endpoint	
Site #	Number of Pts at Site	Vedolizumab	Placebo
U.S. Sites			
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)

.	.	.	.
.	.	.	.
.	.	.	.
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
International Sites			
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)
.	.	.	.
.	.	.	.
.	.	.	.
…	x	n/N (%)	n/N (%)
…	x	n/N (%)	n/N (%)

2. Also, submit an electronic dataset that includes each of the fields in the tables above (in Item 1) by study number, phase (induction or maintenance), and subject identification number.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

_____

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
06/27/2013

From:	Bugin, Kevin
To:	"Costello, Colleen"
Cc:	Bugin, Kevin
Subject:	BLA 125476 vedolizumab - Pending BLA Information Request - June 12, 2013
Date:	Wednesday, June 12, 2013 12:11:23 PM

Hi Colleen,

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for vedolizumab.

We further refer to the first sequence of the BLA submitted on March 27, 2013, which contained information related to Quality. We are reviewing the quality information and have the following requests for information.

(b) (4)

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(b) (4)

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

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/s/

KEVIN B BUGIN
06/12/2013

From: Bugin, Kevin
To: Costello, Colleen
Cc: Bugin, Kevin
Subject: RE: BLA 125476 - Final Submission for Rolling Review
Date: Wednesday, June 05, 2013 2:58:41 PM

Hi Colleen,

Please see below for the response to your additional request for clarification:

Request for clarification:
21 CFR 601.2 and 314.50 require that the marketing application contain a statement "regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter; or was not subject to such requirements in accordance with 56.104 or 56.105."

1. As the Division is aware, several of the clinical studies which will be submitted to the vedolizumab BLA are non-IND foreign studies. Will you please clarify how the before mentioned requirement under 601.2 and 314.50 is applied to non-IND foreign studies that are being included in a marketing application?
   [Bugin, Kevin] Please refer to 21 CFR 312.120 and Guidance for Industry and FDA Staff – FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf).

   a. On April 3, 2009, the Division granted MPI a waiver of the institutional review board (IRB) requirements under 21 CFR Part 56. The scope of the waiver reads to be for foreign studies conducted under the IND. It is unclear if requesting a separate part 56 waiver for the non-IND foreign studies is required or is even an option.
      [Bugin, Kevin] The waiver of the IRB requirements under 21 CFR 56 granted on April 03, 2009, applies to all foreign studies conducted under the IND. For foreign studies not conducted under the IND, a waiver of IRB requirements is not required. However, if you submit foreign studies not conducted under the IND in support of a marketing application, you must ensure that the studies complied with 21 CFR 312.120 which states, in part, that the studies were conducted in accordance with good clinical practice (GCP), including the use of an independent ethics committee (IEC).

      b. Alternately, does the information submitted under 312.120 for acceptance of non-IND foreign data obviate the need for a Part 56 waiver for non-IND foreign studies?
      [Bugin, Kevin] See response above; a waiver of Part 56 does not apply to foreign studies conducted outside of an IND.

Please let me know if you have any further questions.

Kind regards,
Kevin

From: Bugin, Kevin
Sent: Friday, May 31, 2013 10:31 AM
To: Costello, Colleen
Cc: Bugin, Kevin
Subject: RE: BLA 125476 - Final Submission for Rolling Review

Hi Colleen,

I will try to send you response to these questions next week. I am just confirming some of the requirements under 21 CFR 312.120.

In the meantime, I have answered the procedural questions below, in red.

Regards,
Kevin

From: Costello, Colleen [mailto:Colleen.Costello@MPI.com]
Sent: Wednesday, May 29, 2013 3:38 PM
To: Bugin, Kevin
Subject: RE: BLA 125476 - Final Submission for Rolling Review

Dear Kevin –

In follow to our last communication, we continue to work on refining the precise submission date for the last component and hope to have something to you shortly.

In the meantime, we have a couple of questions that I was hoping you could please address for us in the context of the rolling submission/review.

Procedural:

1) Can we expect to receive "Request for Information" (RFI) in advance of receiving the "74 day letter" or the Discipline review letters following FDA's Mid-cycle meeting?
   [Bugin, Kevin] You can expect to receive a "Request for Information" at any time during the review cycle. Issues identified in the "74 day letter" or in "Discipline Review letters" will be issues that rise to the level of "Review Issues." There may or may not be overlaps between the "Requests for Information" and the comments/requests listed in the "74 day letter" or "Discipline Review letter."
2) Can we expect to receive RFIs based on either BLA sequence 0000 or 0001 in advance of "Application Receipt" (Day 0) or "Filing Decision" (Day 60) for the complete application?
   [Bugin, Kevin] Refer to response above, you may receive a Request for Information at any

time, including during filing. I am unaware of any requests being prepared for the first two sequences received to date.

3) Will you be able to acknowledge receipt of the User Fee for this application in advance of the final component being submitted or would we only be notified if the User Fee was not received?
[Bugin, Kevin] The Division does not directly handle the User Fees. It is my understanding that you may submit the User Fee payment at any time in advance and that some sort of receipt is provided. You may contact the User Fee Staff for additional information. They may be reached at (301) 796-3602.

Request for clarification:

21 CFR 601.2 and 314.50 require that the marketing application contain a statement "regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter; or was not subject to such requirements in accordance with 56.104 or 56.105."

1. As the Division is aware, several of the clinical studies which will be submitted to the vedolizumab BLA are non-IND foreign studies. Will you please clarify how the before mentioned requirement under 601.2 and 314.50 is applied to non-IND foreign studies that are being included in a marketing application?
    a. On April 3, 2009, the Division granted MPI a waiver of the institutional review board (IRB) requirements under 21 CFR Part 56. The scope of the waiver reads to be for foreign studies conducted under the IND. It is unclear if requesting a separate part 56 waiver for the non-IND foreign studies is required or is even an option.
    b. Alternately, does the information submitted under 312.120 for acceptance of non-IND foreign data obviate the need for a Part 56 waiver for non-IND foreign studies?

Thank you in advance for the clarification.

Regards,
Colleen

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
06/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 009125

MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Karen D. Quinn, Ph.D.
Director, Worldwide Regulatory Affairs CMC
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Quinn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN0002 (vedolizumab).

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2012. The purpose of that meeting was a pre-BLA CMC only meeting.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Joel Welch, Regulatory Project Manager at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
CMC Team Leader
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	pre-BLA (CMC only)
Meeting Date and Time:	November 13, 2012; 1:00 p.m.
Meeting Location:	White Oak Campus, Bldg 22, Conf Room 1315
Application Number:	IND 009125
Product Name:	Vedolizumab
Indication:	ulcerative colitis (UC) and Crohn's Disease (CD)
Sponsor/Applicant Name:	Millennium Pharmaceuticals, Inc.
Meeting Requestor:	Karen Quinn
Meeting Chair:	Marjorie Shapiro
Meeting Recorder:	Joel Welch

FDA Participants:
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

Kurt Brorson, Ph.D.	Product Quality Reviewer
Gerald Feldman, Ph.D.	Product Quality Reviewer
David Frucht, M.D.	CMC Team Leader
Marjorie Shapiro, Ph.D.	CMC Team Leader
George Miesegaes, Ph.D.	Product Quality Reviewer
Joel Welch, Ph.D.	Regulatory Health Project Manager

Office of Compliance
Office of Manufacturing and Product Quality
Biotechnology Manufacturing Assessment Branch

Colleen Thomas, Ph.D.	Microbiology Reviewer
Lakshmi Narasimhan, Ph.D.	Microbiology Reviewer
Patricia Hughes, Ph.D.	Team Leader

Office of New Drugs
Office of Drug Evaluation III
Division of Gastroenterology and Inborn Error Products

Kevin Bugin	Senior Regulatory Health Project Manager
Anil Rajpal, M.D.	Clinical Team Leader

Millennium Pharmaceuticals, Inc.

Karen D. Quinn, Ph.D.	Director, Global Regulatory Affairs CMC
Norbert Schuelke, Ph.D.	Director, Biologics Process Development

Liz Spinella	Associate Director, Commercial Quality Operations,
Eva Barbarics, Ph.D.	Sr. Scientist II, Analytical Development Biologics
Anne Kowal, Ph.D.	Director, Analytical Development Biologics
Willow DiLuzio, Ph.D.	Associate Director, Biologics Formulations
Paul Hanson, Ph.D.	Sr. Engineer II, Biologics Process Development
Colleen Costello, Ph.D.	Sr. Director, Global Regulatory Affairs
Anne Bailey, M.S.	Global Regulatory CMC, Associate Director (Takeda)

1.0 BACKGROUND

MLN0002 (vedolizumab) is a humanized IgG1 monoclonal antibody to the human $\alpha_4\beta_7$ integrin. MLN0002 is administered via intravenous infusion and is currently in development for treatment of ulcerative colitis (UC) and Crohn's Disease (CD). On September 10, 2012 Millennium Pharmaceuticals Inc. requested a CMC only, pre-BLA meeting. The Agency granted the meeting request on October 5, 2012. The Agency provided preliminary responses to the Sponsor's questions on November 9. Those responses appear in italics in section 2.

2.0 DISCUSSION

Sponsor Question 1:
In the initial BLA, the Sponsor is proposing a 36 month shelf life for MLN0002 drug product (DP) at 2-8°C. The initial dossier will contain stability from two lots with 24 months and two lots with 36 months. The Sponsor believes that these stability data, demonstrating that MLN0002 DP is stable and remains within specifications when stored at 2-8°C for up to 36 months with no degradation observed, combined with the observed stability at accelerated conditions, justify a 36 month shelf life. Does the Agency agree that these data could be used to justify a 36 month shelf life?

The Sponsor also requests the opportunity to provide additional stability data to support the shelf life during the dossier review.

FDA Response: Your proposal of a 36 month shelf life for vedolizumab Drug Product based on data from 2 lots of Drug Product stored for 36 months at 2-8°C and another 2 lots of Drug Product stored for 24 and 30 months at 2-8°C (with supporting data from accelerated stability studies) is acceptable in principle. Please clarify the nature of the stability update proposed. Under PDUFA V, a BLA must be complete at the time of submission. However, data may be submitted to the BLA in response to an information request.

<u>Additional Discussion During Meeting:</u>
The Sponsor provided a summary of the stability data they plan to include at the time of BLA filing (slide 3 of the attached presentation), as well their proposed stability update within 30 days of submission. The Sponsor also noted that their submission date is still tentative and subject to

change based on input from their clinical colleagues. The Agency stated that the stability update as presented by the Sponsor is acceptable. Additionally, the Agency noted that should the timing of the stability update fall outside the 30 day window, an information request may be submitted to Millennium to request the data.

Sponsor Question 2:
The proposed testing methods for release testing for the commercial drug substance (DS) and drug product (DP) are provided. The approach for determining the acceptance criteria is included. An example of this approach is provided.

Does the Agency agree with the testing methods proposed for commercial testing of the DS and the DP and the proposed approach for determining the acceptance criteria?

FDA Response: Your proposed release tests for vedolizumab commercial Drug Substance and Drug Product appear to be acceptable. We agree with your plans (b) (4) *subsequently remove these tests from lot release. You propose to remove* (b) (4) *for determination of vedolizumab potency. Please provide a greater justification to remove this assay based on comparative data obtained for all lots released to date. Final determination as to whether its removal is appropriate will be a review issue.* (b) (4) (b) (4) *Noting that you already have close to 30 lots of Drug Substance and 20 lots of Drug Product, we do not necessarily agree with this approach. Please provide the acceptable range for each assay as determined by the use of* (b) (4) *For comparative purposes the use* (b) (4) *The determination of the appropriate acceptance criteria for each individual assay should be based on ICHQ6b including historical knowledge of the assay as well as the most appropriate method of range determination*

<u>Additional Discussion During Meeting:</u>
The Sponsor asked what specific data the Agency would require in order to support the removal of the adhesion assay and to replace it with only the ELISA binding assay. The Agency stated that while the adequacy of the data itself will be a review issue, the data needs to be sufficient to demonstrate that the two assays provide comparable information. Specifically, since the (b) (4) provides more information than merely binding, adequate information should demonstrate that the ELISA assay provides as sensitive of a test. For this reason, the data should be comprehensive, and include release testing and even stressed samples.

The Sponsor stated they agreed to provide the range from the (b) (4) and for comparison, three standard deviations for the acceptance criteria. The Sponsor also noted that the acceptance criteria should also reflect that only a limited number of (b) (4) lots have been used to date, and that several tests have results which lack a normal distribution. The Agency reminded the Sponsor the final decision on acceptance criteria will be a review issue and suggested it might be useful to include a history of how the specification evolved over time as part of the BLA. The Sponsor agreed.

Sponsor Question 3:
The approach for determining extractable/leachable information is provided. Does the Agency agree with our approach?

FDA Response: Your approach for determining extractable/leachable information is acceptable.

Additional Discussion During Meeting:
There was no additional discussion.

Sponsor Question 4:
The Sponsor is considered including a Comparability Protocol for the (b) (4) of the drug product manufacturing process at the commercial manufacturer, (b) (4) Does the Agency agree that the information as described is sufficient information for the inclusion of the comparability protocol in the BLA?

FDA Response: Your proposal to include a Comparability Protocol for the (b) (4) of vedolizumab Drug Product manufacture at (b) (4) is acceptable. The acceptability of the full protocol will be a review issue.

Additional Discussion During Meeting:
There was no additional discussion.

Sponsor Question 5:
The (b) (4) procedure for the drug substance (DS) (b) (4) The Sponsor believes that revalidation of the (b) (4) lifetime study will be sufficient to implement this improvement into commercial DS manufacturing. Does the Agency agree?

FDA Response: Your proposal to use the revalidation of the (b) (4) study to allow implementation of a revised (b) (4) may be acceptable providing (b) (4) is adequately defined, justified, and agreed upon prior to implementation.

Additional Discussion During Meeting:
The Sponsor clarified that the (b) (4) (b) (4). The Agency asked if these were (b) (4) The Sponsor indicated yes. The Agency indicated it agreed with the approach and that the information describing their approach should be included in the BLA.

Additional FDA Comments:

The CMC Drug Substance section of your BLA (Section 3.2.S) should include the following product quality microbiology information:

(b) (4)

[redacted]

The CMC Drug Product section of your BLA (Section 3.2.P) should include validation data summaries supporting the (b) (4) process and sterility assurance. For guidance on the types of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

- The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

(b) (4)

[redacted]

- The following method validation information should be provided:
  - Container closure integrity testing (3.2.P.2.5). System integrity (b) (4) should be demonstrated for the complete manufacturing process including shipping. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
  - Qualification data for bioburden, sterility and endotoxin test methods performed for (b) (4) (if applicable) and the drug product, as appropriate (3.2.P.5).

<u>Additional Discussion During Meeting:</u>
The Sponsor thanked the Agency for the comments. The Sponsor inquired if their approach to validate hold time for bioburden and endotoxin by (b) (4) The Agency indicated no, even (b) (4) The Agency stated that this approach can be appropriate for determining biochemical stability of samples during hold conditions, (b) (4) The Agency stated validation must demonstrate microbial control (b) (4). The Agency stated too little information was provided to give specific recommendations to the Sponsor on how to conduct the study, but that the firm should focus on validating hold times (b) (4)

The Sponsor asked for clarification regarding the drug product hold time validation as well. The Agency stated that like the drug substance, the drug product hold time (b) (4) The Agency agreed to provide literature citations to the Sponsor to discuss this topic further.

Regarding shipping validation, the Sponsor indicated that studies will be performed (b) (4) . The Agency stated this proposal appears acceptable. The Agency reminded the Sponsor that normal shipping times need to be established and acceptable excursion limits based on supporting data should be established.

Finally, the Sponsor noted that for container closure integrity testing, stability samples were shipped from (b) (4) The Sponsor asked if this was acceptable. The Agency stated it was.

Endotoxin References

1. Mueller M, et al. 2004 Aggregates are the biologically active units of endotoxin. J.Biol.Chem., 279, 26308-26313
2. Kim Boweres and Lynn Tran 2011 Creation of an in-house naturally occurring endotoxin preparation for use in endotoxin spiking studies and LAL sample hold time analysis. American Pharmaceutical review 14(6)
3. Mark et al. 2001 Removal of tightly bound endotoxin from biological products. J. Biotech 88 67-75
4. Kannegieter, E.M. and Baggerman, C 1984 A new method to reduce electrolyte inhibition of the detection of endotoxins in large volume parenterals J.PDA.org.38: 17-20

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- The Agency agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
  - Primary Stability Lots manufactured at (b) (4) – additional stability time point s of:
    - 1 lot at 30 and 36 months
    - 1 lot at 36 months
  - DP validation lots – additional stability time points for:
    - 3 lots up to and including 6 months

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER LATE COMPONENT - QUALITY

4.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

5.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

6.0 ACTION ITEMS

There were no action items.

7.0 ATTACHMENTS AND HANDOUTS

The Sponsor used a slide presentation to guide the discussion. Those slides are presented as an attachment.

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/s/

MARJORIE A SHAPIRO
12/07/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 009125

MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Colleen Costello, Ph.D.
Director, Regulatory Affairs
35 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN0002 (vedolizumab).

We also refer to the meeting between representatives of your firm and the FDA on November 06, 2012. The purpose of the meeting was to discuss the content and format of a complete Biologics License Application (BLA) for vedolizumab for the treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD), who have had an inadequate response with, lost response to, or were intolerant to 1 or more conventional therapies, including tumor necrosis factor-alpha (TNFα)..

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, MS, RAC
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: November 06, 2012, from 3:00 to 4:00 p.m., EST
Meeting Location: 10903 New Hampshire Ave,
White Oak Building22, Conference Room 1313,
Silver Spring, MD 20903

Application Number: IND 009125
Product Name: Vedolizumab
Indication: Ulcerative colitis/Crohn's disease
Sponsor/Applicant Name: Millennium Pharmaceuticals, Inc.

Meeting Chair: Anil Rajpal
Meeting Recorder: Kevin Bugin

FDA Attendees:
Julie Beitz, M.D., Director, Office of New Drug Evaluation III (ODEIII)
Victoria Kusiak, M.D., Deputy, ODEIII, Deputy, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Donna Griebel, M.D., Director, Andrew Mulberg, MD, FAAP, CPI, DGIEP
Joyce Korvick, MD, MPH, Safety Deputy, DGIEP
Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP
Klaus Gottlieb, MD, MBA, MS, RAC, Medical Officer, DGIEP
Sushanta Chakder, PhD, Nonclinical Team Leader, DGIEP
Tamal Chakraborti, PhD, Nonclinical Reviewer, DGIEP
Kevin Bugin, MS, RAC, Senior Regulatory Health Project Manager, DGIEP
Anissa Davis, RN, BSN, Regulatory Health Project Manager, DGIEP
John Yap, PhD, Statistics Reviewer, OB, DB7
Brad McEvoy, PhD, Statistics Reviewer, OB, DB7
Milton Fan, PhD, Statistics Reviewer, OB, DBIII
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology, (OCP)
Lucy Fang, PhD, Clinical Pharmacology Reviewer, OCP
Sally Yasuda, MD, Division of Neurology Products (DNP)
Lisa Jones, MD, DNP
David Shih, MD, MS, FACPM, Team Leader, Office of Safety and Epidemiology (OSE), Office of Pharmacovigilance and Epidemiology (OPE), Division of Epidemiology 1

Kendra Worthy, MD, OSE, Division of Risk Managment

Sponsor Attendees:

Millennium Pharmaceuticals Participants:

Melody Brown - Vice President, Regulatory Affairs
Colleen Costello, Ph.D.-Senior Director, Regulatory Affairs
Eric Fedyk Ph.D. - Director, Pharmacology & Toxicology
Irving Fox, M.D., CM, FRCP- Distinguished Scientific Fellow, Clinical Development
Mingxiu Hu Ph.D-Senior Director, Biostatistics & Statistical Programming
Veronique Kugener, M.D., MSc, MBA - Vice President, Pharmacovigilance & Risk Management
Catherine Milch M.D., M.S. - Medical Director, Clinical Development
Maria Rosario, Ph.D. – Director, Clinical Pharmacology
Serap Sankoh Ph.D. - Director, Biostatistics
Veit Schmelmer, Ph. D - Senior Director, Drug Development Management
Jing Xu Ph.D. - Director, Biostatistics

Takeda Pharmaceutical Participants

Asit Parikh, M.D., PhD, Vice President General Medicine
Lesley Wise, Ph.D., Senior Director, Global PV Risk Management
Bagyashree Sundaram - Associate Director, Regulatory Affairs
Reema Mody, MBA, Ph.D. - Associate Director, Global Outcomes Research - GI/GU

1.0 BACKGROUND

On August 24, 2012, Millennium Pharmaceuticals, Inc., (Sponsor) requested a Type B, Pre-BLA meeting with the Division of Gastroenterology and Inborn Errors Products (DGIEP, the Division). The purpose of the meeting was to discuss the content and format of a complete Biologics License Application (BLA) for vedolizumab for the treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD), who have had an inadequate response with, lost response to, or were intolerant to 1 or more conventional therapies, including tumor necrosis factor-alpha (TNFα). The meeting was granted and scheduled for October 30, 2012. Due to inclement weather and government closures, the meeting was rescheduled to November 06, 2012. The meeting took place on November 06, 2012.

2. DISCUSSION

Clinical Development

Question 1

Based on advice received at the July 2012 Type C meetings, the sponsor intends to submit the BLA for vedolizumab in March 2013, so that the majority of the safety database requested by the Division is available for the Day 120 Safety Update. Preparation of the BLA is ongoing and is based on a safety database cutoff date of 16 July 2012, which is approximately 8 months prior to submission. Does the Division agree with the safety database cutoff proposal for the initial BLA submission?

FDA Response:

Due to the new requirements under PDUFA V for applications under the "Program", we cannot agree with your proposal. Your safety database at the time of original BLA submission must include data on at least 900 patients that received ≥ 24 infusions (with a minimum of 4 weeks of follow-up after the last infusion).

Sponsor Response:

The Sponsor requests to discuss FDA's Response at the meeting on Nov 6th. Specifically, the Sponsor would like to gain agreement on what constitutes a "complete submission" for this product.

Discussion:

The Division referred the Sponsor to the PDUFA V Goals letter (see http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf). The Division noted that a complete application should include, for example, required long-term safety data. The Division also noted that our position regarding the safety database requirements stated in the response to this question was discussed with Senior Management in OND.

Question 2

At the July 2012 Type C meetings, the Division stated that safety data from at least 900 patients who received ≥ 24 infusions (with a minimum of 4 weeks of follow-up after the last infusion) would be required to conduct a review and present to an Advisory Committee. The Sponsor proposes to provide these data in the 120-Day Safety Update Report. In the event that the requisite 900 patients are not obtained at the time of the 120-Day Safety Update data cut, the following will be provided:

a. The first safety update during the BLA review will be the 120-Day Safety Update Report. This report will be a complete update of the safety database in compliance with 21 CFR 314.50(d)(5)(vi)(b). The second safety update, if needed, will be the Supplemental Safety Report. This report will comprise updated safety information. The database cutoff date for the Supplemental Safety Report will be determined once 900 patients have received ≥ 24 infusions (with a minimum of 4 weeks of follow-up after the last infusion), and is projected to be in May 2013. The data from this cutoff date will be submitted as a Supplemental Safety Report as an appendix to the 120-Day Safety Update Report in July 2013. Is this approach acceptable?

b. Further, it is the sponsor's understanding that the Supplemental Safety Report will not be considered a major amendment to the application and will not result in a delay in the PDUFA date for the application. Does the Division agree?

FDA Response:

See Response to Question 1 above.

Sponsor Response:

The Sponsor requests to discuss FDA's Response at the meeting on November 6th.

Discussion:

See discussion for Question 1.

Question 3

The sponsor intends to submit a single integrated summary of safety (ISS) in the BLA to support the indications for UC and CD. Accordingly, the safety analyses for vedolizumab will be presented by indication (UC and CD) and combined as described below. Does the Division agree?

FDA Response:

We agree. The safety analyses for vedolizumab may be combined but also need to be presented by individual indication (UC vs. CD).

Sponsor Response:
The sponsor would like to provide additional clarification based on the FDA Response. All data in the ISS will be presented by individual indication (UC or CD) and then combined (UC and CD).

Using these broad headings, the integrated safety summary document will include the data organized first by "topic" for major components of the safety data (e.g. common adverse events, serious adverse events, adverse events causing discontinuations, etc.) and then by indication (e.g. UC, CD, Combined).

Further, the sponsor would like to note that safety data specific to the UC Induction study will not be presented separately in the ISS as these data are presented in the C13006 CSR. However, safety data specific to the CD Induction studies is presented in the ISS as an integrated analysis of Study C13007 and C13011.

Is this approach acceptable?

FDA PreMeeting Response:
Please explain how data from Study C13008 will be presented. The Sponsor provided clarification on the presentation of this data and the Division finds the approach acceptable.

Question 4
In the BLA for vedolizumab, the sponsor intends to submit a single Section 2.7.4 Summary of Clinical Safety (SCS), which will contain safety information for both CD and UC, separately and in aggregate. Is this acceptable to the Division?

FDA Response:
Submission of a single Section 2.7.4 Summary of Clinical Safety (SCS), which will contain safety information for both CD and UC, separately and in aggregate, is acceptable to us.

Sponsor Response:
No further discussion requested.

Question 5
As requested by the Division at the Type C meetings in July 2012, the sponsor will provide a Monthly Exposure Update Report (MEUR) with the pre-BLA briefing book, with the original BLA submission, and monthly thereafter up to the time of the Advisory Committee meeting. The MEUR will include updated exposure numbers in the format prescribed by the Division in the July 2012 Type C Meeting Minutes. Given that each MEUR will consist of the 4 tables requested by the Division and provide monthly updates

of exposure, Millennium wants to confirm with the Division that submission of the MEURs only will not be considered a major amendment to the application and will not result in a delay in the PDUFA date for the application. Does the Division agree?

FDA Response:
We agree. Submission of the MEURs only will not be considered a major amendment to the application.

Sponsor Response:
The Sponsor requests to discuss FDA's Response at the meeting on November 6th.

Discussion:
The MUER is no longer applicable; see discussion for Question 1. The 120-day safety update is still required.

Question 6
The sponsor plans to submit narratives in the BLA for all patients who experienced at least 1 SAE except for SAEs of disease exacerbation considered unrelated to study drug defined as: SAEs with a preferred term "colitis ulcerative" or "Crohn's disease" that were deemed unrelated by the investigator and did not result in study discontinuation or death. The SAEs of disease exacerbation unrelated to study drug will be provided in tabular format. Does the Division agree with this approach?

FDA Response:
Your proposal is acceptable. However, you should be prepared to provide the narratives for SAEs of disease exacerbation considered unrelated to study drug defined as: SAEs with a preferred term "colitis ulcerative" or "Crohn's disease" that were deemed unrelated by the investigator and did not result in study discontinuation or death, if this information is deemed necessary during the review.

Sponsor Response:
No further discussion requested.

Question 7
The sponsor intends to submit one integrated summary of efficacy (ISE) for CD and one for UC to the BLA. The content and format of the ISEs will mirror the content and format of the summaries of clinical efficacy (SCEs). Is this approach acceptable?

FDA Response:

The approach outlined in your position statement appears acceptable to us. However, while you may pool the data from different studies for your integrated analyses, the presentation in your tables should also include the results of the individual studies juxtaposed to the combined analysis.

Sponsor Response:
No further discussion requested.

Question 8

At the End of Phase 2 meeting (June 2008), the sponsor indicated that a patient reported outcomes (PRO) dossier for both Crohn's Disease Activity Index (CDAI) and Mayo score would be submitted with the BLA submission. Since then, a comprehensive review of available literature and regulatory precedents has provided sufficient evidence regarding the robustness of both of these disease activity indices for use as the primary and secondary efficacy endpoints in the pivotal studies for UC and CD. The following information will be included as appendices to the pivotal Clinical Study Reports (CSRs) in the BLA submission:

a. Literature review supporting the use, validation and robustness of the CDAI and Mayo Score.

b. Equivalency report comparing electronic interactive voice response (IVR) to paper-based assessments for the patient components of the CDAI and Mayo scores.

c. Language translation and cultural adaptation reports for both instruments.

The sponsor believes that this information provides sufficient documentation supporting the robustness and appropriateness of the patient components for both the CDAI and Mayo scoring instruments, removing the need for a PRO dossier for either index. Is this acceptable to the Division?

FDA Response:

We acknowledge that you will not be submitting a PRO dossier with this application to support the patient components of the CDAI and Mayo scoring instruments. We cannot agree that items a, b and c will be adequate to support labeling based on the patient components of these scoring instruments.

Sponsor Response:
All primary and secondary endpoints for the phase 3 clinical studies C13006, C13007, C13011, and C13008 are based on either the total score or the score from objective components of the instruments (Mayo score or CDAI). Further, no primary or secondary endpoints in the aforementioned phase 3 studies are based solely on patient reported components of either

instrument (Mayo score or CDAI). The Sponsor requests clarification of FDA's response and discussion at the meeting on November 6, 2012.

Discussion:
The Division clarified that the inclusion of these endpoints in labeling will be a review issue.

Question 9
With respect to its obligations under Pediatric Research Equity Act (PREA), the sponsor intends to request a deferral of clinical investigation in children between (b) (4) years of age until the post marketing period and a waiver of studies in children (b) (4) of age. The sponsor proposes to include the request for deferral and waiver as part of the BLA. Does the Division agree with this plan?

FDA Response:
Your proposal appears reasonable but will be subject to review by the Office of New Drugs Pediatric Review Committee (PeRC).

Please be aware that the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) changes the timeline for submission of a PREA Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

Sponsor Response:
The sponsor requests clarification if it is required to reach agreement with the PeRC at FDA, independent from this agreement with the Division outlined in the FDA Response.

Discussion:
The Division will consult with PeRC as part of the review for your application.

The Sponsor asked whether or not it was acceptable to submit their pediatric study plan at the time of the BLA submission. The Division referred the Sponsor to the FDA's preliminary response and suggested the Sponsor contact the Pediatric Team for further guidance at pedsdrugs@fda.hhs.gov.

Clinical Pharmacology

Question 10
The sponsor believes that the clinical pharmacology package is adequate to support the BLA for use in the proposed patient populations. Does the Division agree?

FDA Response:

The contents outlined in the clinical pharmacology package may be adequate to support the filing of the intended BLA submission; however, we have the below general comments for your consideration:

1) **Provide adequate clinical pharmacology data to justify the proposed dosing regimen for labeling.**
2) **Your product is intended to treat chronic disease conditions that may have increased levels of proinflammatory cytokines which can suppress the formation of CYP450 enzymes. Therefore, improvement of disease condition following treatment with your product could normalize the formation of CYP450 enzymes. Please develop a strategy to address the potential drug-drug interactions between your product and concomitant medications which are metabolized by CYP450 enzymes.**
3) **Evaluate the impact of immunogenicity of your to-be-marketed product on pharmacokinetics/pharmacodynamics, efficacy, and safety of your product. Submit the analysis datasets.**
4) **If you intend to submit model-based population analyses (i.e., modeling and simulation) in the clinical pharmacology section, submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:**
    - **All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
    - **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).**

Items 1, 3 and 4 above are required at the time of initial submission of your application.

In addition to Summary of Clinical Pharmacology Findings in the eCTD submission, we request at the time of application submission that you provide a Clinical Pharmacology Summary as a review aid according to the format provided in Appendix 1. The review aid will allow us to perform the regulatory review more efficiently and in a timely manner.

Sponsor Response:

The sponsor has developed a rationale for the proposed dosing regimens, and it will be included in the BLA package. The strategy regarding the assessment of drug-drug interaction potential of vedolizumab will be included in the BLA package. All datasets requested will be included in the BLA package.

The sponsor acknowledges the requested information as outlined in the FDA Response to Question 10. The sponsor requests clarification regarding the location of the Clinical Pharmacology Summary document in the eCTD structure.

FDA PreMeeting Response:

FDA clarified that the review aid for clinical pharmacology can be submitted under Section 1.11.3 Efficacy Information in the eCTD or 2.7.2 Summary of Clinical Pharmacology Studies.

Risk Management Plan

Question 11

Pursuant to the Type C meeting held on July 24 and 25 2012, Millennium will submit a proposed Risk Evaluation and Mitigation Strategy (REMS) with the initial BLA. Does the Division agree with this approach?

FDA Response:

Your proposal to submit a proposed REMS for vedolizumab with the initial BLA is acceptable.

Sponsor Response:

No further discussion requested.

Labeling

Question 12

The vedolizumab phase 3 clinical program for both UC and CD includes more than 2700 patients exposed to vedolizumab. Approximately 50% of the patients who have received vedolizumab have received concomitant corticosteroids and approximately 30% of these patients have continued to use immunomodulators during the course of their participation in the phase 3 studies. The sponsor believes that the efficacy and safety data (b) (4) are adequate to support the evaluation and to seek a label claim of (b) (4) Does the Division agree?

FDA Response:

No. (b) (4)

(b) (4)

(b) (4)

[redacted]

Sponsor Response:
No further discussion requested.

Question 13
The safety and efficacy of vedolizumab dosed 300 mg Q4W or 300 mg Q8W have both been explored in pivotal phase 3 studies. The proposed dose regimen is 300 mg administered as an intravenous infusion over 30 minutes at Week 0, Week 2, Week 6, then every 8 weeks thereafter. If there is an inadequate response to the 300 mg every 8 weeks treatment and the treatment is well tolerated, then the treatment frequency may be increased to 300 mg every 4 weeks. Does the Division agree that the proposed analyses will provide sufficient data to support a review of the proposed dosing regimens?

FDA Response:
Although the data may be sufficient to evaluate the efficacy of each of the two dosing regimens, our current thinking is that the data are not sufficient to evaluate the efficacy of dose escalation (to the Q 4 weeks regimen) in patients that had an inadequate response (to the Q 8 weeks regimen), and thus will not support the proposed dose escalation recommendation in the label. It appears that in the studies conducted, patients that had an inadequate response to the Q 8 weeks regimen were not re-randomized to remaining on the Q 8 weeks regimen versus escalation to the Q 4 weeks regimen.

Sponsor Response:
No further discussion requested.

Question 14
The sponsor will submit the draft labeling in Structured Product Labeling (SPL) within 14 days of submission of the BLA. Does the Division agree?

FDA Response:
We consider the submission of the draft label in Structured Product Labeling (SPL) a minor component of the application and agree with your proposal to submit within 14 days of submission of the BLA.

Sponsor Response:
No further discussion requested.

Statistics

Question 15

As outlined at the Type C meeting in July 2012, the sponsor intends to submit Case Report Tabulation (CRT) as part of the BLA package. The CRT will include documentation of data (define.xml) and Study Data Tabulation Model (SDTM) for all clinical studies: L297-005, L297-006, L297-007, L299-016, M200-021, M200-022, C13001, C13002, C13004, C13005, C13006, C13007, C13008, C13009, C13010, C13011, C13012, and C13013. In addition, the sponsor plans to submit Analysis Data published in scientific data set (SDS) 1.6 format along with Source Data published in SDS 1.6 format. Does the Division agree?

FDA Response:

We agree, and in addition please provide the following for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to include at the time of your initial BLA submission:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.

2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm). We recommend that the data definition file comply with the latest CDISC/Define.XML standard.

3. A well commented and organized software program written for each analysis dataset and efficacy table created.

Sponsor Response:

The sponsor requests clarification if it is required to reach agreement with the eData support team at FDA, independent from this agreement with the Division outlined in the FDA Response.

Further, the sponsor proposes not to include dataset formatted in CDISC/ADaM listed in Item 2 above and in Appendix 2, Part III of these Preliminary Meeting Minutes (p. 24). Does the FDA agree?

Finally, with respect to Item (1) above, the Sponsor refers FDA to the position statement for Question 1 and confirms that all clinical data from the completed clinical studies have been cleaned and the database locked. In addition, the database from the open label safety study, C13008, remains open and has not been locked.

Discussion:
The eData support team has participated in the agreements made herein. While CDISC-formatted data are encouraged, they are not yet required. Therefore it is acceptable to submit your legacy-formatted data. We also agree that it would be acceptable for C13008 to remain open and unlocked.

Regulatory

Question 16
It is the sponsor's opinion that the results from the adequate and well-controlled pivotal study (C13006) and a double-blind, placebo-controlled supportive phase 2 study (M200-022) with supportive evidence from multiple phase 1 and phase 2 studies provide substantive evidence for the treatment of patients with moderately to severely active UC. The sponsor believes that the results from these studies are adequate for review and potential approval in a BLA. The clinical program and study results were summarized in the meeting package submitted on 21 June 2012 (SN 0461), which is referenced herein, and discussed with the Division at the Type C meeting in July 2012. Does the Division agree?

FDA Response:
Whether the data from the above referenced studies provide substantive evidence for efficacy and safety in the treatment of patients with moderately to severely active UC will be a review issue.

We would also like to refer you to our answers to similar questions documented in the minutes of the Type C meeting meetings between Millennium and the FDA on July 24, 2012, and July 25, 2012. Our position has not changed since those meetings.

Sponsor Response:
No further discussion requested.

Question 17
It is the sponsor's opinion that the results from the adequate and well-controlled pivotal study (C13007) and a double-blind, placebo-controlled supportive phase 3 study (C13011) with supportive evidence from multiple phase 1 and phase 2 studies provide substantive evidence for

the treatment of patients with moderately to severely active CD. The sponsor believes that the results from these studies are adequate for review and potential approval in a BLA. The clinical program and study results were summarized in the meeting package submitted on 21 June 2012 (SN 0461), which is referenced herein, and discussed with the Division at the Type C meeting in July 2012. Does the Division agree?

FDA Response:
Whether the data from the above referenced studies provide substantive evidence for efficacy and safety in the treatment of patients with moderately to severely active CD will be a review issue.

We would also like to refer you to our answers to similar questions documented in the minutes of the Type C meeting meetings between Millennium and the FDA on July 24, 2012, and July 25, 2012. Our position has not changed since those meetings.

Sponsor Response:
No further discussion requested.

Question 18
The sponsor seeks agreement on the following BLA content and format topics:

a. The sponsor intends to submit 1 BLA under 1 BLA number encompassing both of the proposed indications. Is this approach agreeable to the Division?

b. In the BLA, the sponsor intends to submit copies of all references cited in pivotal or supporting CSRs, and important references for earlier studies. Other references will be available upon request during the review. Does the Division agree with this approach?

c. The sponsor plans to submit the planned BLA in eCTD using US (ver. 2.01), ICH (ver. 3.2), and STF (ver. 2.2) Document Type Definition files (DTDs). Is this acceptable?

d. The BLA will be submitted utilizing the International Nonproprietary Name (INN) while the trade name is undergoing review and approval under BB-IND 9125. Does the Division agree with this approach?

e. The sponsor will provide a comprehensive technical report that addresses the mechanism of action of vedolizumab relative to natalizumab. This report will incorporate all nonclinical and clinical data available. The report will reside in Modules 4 and 5. Does the Division agree with the location of the report within the BLA?

FDA Response:

a) Submission of a single BLA is acceptable.

b) Your proposal for submission of the reference literature is acceptable.

c) Your plans for submission in eCTD format and the versions you propose are acceptable.

d) The use of International Nonproprietary Name (INN) is acceptable.

e) While you propose to incorporate clinical data, it appears that the majority of the mechanism of action information will be supported by non-clinical data. The technical report should go into Module 4 with some cross-references to Module 5.

Sponsor Response:

In response to FDA Response to item (e), the sponsor would like to clarify that a significant amount of clinical data has been generated in support of the mechanism of action of vedolizumab. As such, the sponsor prefers to provide the comprehensive technical report in both Module 4 and 5 of the BLA. Is this approach acceptable?

FDA PreMeeting Response:

Your approach is acceptable.

Question 19

The sponsor believes there are no outstanding regulatory commitments pertaining to IND 9125. Does the Division agree?

FDA Response:

Please clarify the outstanding regulatory commitments pertaining to IND 9125 that you are referring to.

FDA has no other outstanding questions for the sponsor prior to the BLA submission at this time.

Sponsor Response:

The sponsor is not aware of any outstanding regulatory commitments pertaining to IND 9125.

Additional Discussion:

See Sponsor's attached presentation—the Sponsor wishes to obtain feedback from the Division regarding the suitability of filing for a priority review designation.

The Division noted that the determination of priority or standard review will be made at the time of filing of the BLA.

Appendix 1: Clinical Pharmacology Summary

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a **stand-alone word document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable.
Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the exposure-response relationship for both efficacy and safety of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 What are the characteristics of drug metabolism?

2.5.7 What are the characteristics of drug elimination in urine?

2.5.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.9 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in

healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Body Weight

2.6.2.3 Elderly

2.6.2.4 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population

indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment

2.6.2.7 Hepatic Impairment

2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.2 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.3 Does the label specify co-administration of another drug?

2.7.4 What other co-medications are likely to be administered to the target population?

2.7.5 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

2.8.1 Was the manufacturing process changed during the development program? (Include a table listing all the products used throughout the clinical development programs.)

2.8.2 Was the proposed to-be-marketed formulation comparable to the formulation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?

2.9 Analytical Section

2.9.1 What bioanalytical methods are used to assess therapeutic protein concentrations?
Briefly describe the methods and summarize the assay performance. Please provide tables for each assay to address the below questions

2.9.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?
For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.1.2 What are the lower and upper limits of quantitation?
For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.1.3 What are the accuracy, precision, and selectivity at these limits?
For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.1.4 What is the sample stability under conditions used in the study?
For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide

information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

2.9.1.5 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.2 What bioanalytical methods are used to assess the pharmacodynamic markers? Briefly describe the methods and summarize the assay performance.

2.9.3 What bioanalytical methods are used to assess the immunogenicity? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference (including drug interference) and matrix, etc.

2.9.3.1 What is the performance of the binding anti-product antibody assay(s)?

2.9.3.2 What is the performance of the neutralizing assay(s)?

Appendix 2: OSI Pre-BLA Request – IND 9125 Vedolizumab

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

Sponsor Response:
The sponsor requests clarification regarding the location of the document addressing Part I (#1 - #5) in the eCTD structure (p 23 of the Preliminary Meeting Minutes).

FDA Response:
As we note in responses to the following questions, items in response to Part I (#1-#5) are requested to be provided in pdf format. The recommended eCTD formatting is provided in Attachment 2. If further clarification regarding eCTD formatting for BIMO items is still needed, we recommend contacting the CDER Electronic Submission (CDER ESUB) Support Team at esub@fda.hhs.gov.

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

Sponsor Response:
The sponsor requests clarification that submission of information formatted in Microsoft Excel® is acceptable. Further, the sponsor requests clarification that the scope of this request is the completed Phase 3 clinical studies (C13006, C13007, and C13011).

FDA Response:
Per the eData team, excel is acceptable. However, we request that this information be provided in a .pdf file format for each study that is considered pivotal to the Agency's determination of efficacy and safety (C13006, C13007, and C13011).

Sponsor Response:
For Item 1(d), information pertaining to the current location of PIs that are no longer at the clinical site and have not retained study related responsibilities in the aforementioned completed phase 3 studies will not be provided as this information was not collected or tracked by the sponsor.

FDA Response:
Regarding PIs that are no longer at the clinical site and have not retained study related responsibilities, your proposal is acceptable. The site number, PI name, address, and contact information available should still be provided (Items 1. a-c.). If available, FDA would appreciate your noting the name/address/contact information of the individual that has assumed study related responsibilities/control of study related documents from the original PI.

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

Sponsor Response:
The sponsor requests clarification that submission of information formatted in Microsoft Excel® is acceptable. Further, the sponsor requests clarification that the scope of this request is the completed Phase 3 clinical studies (C13006, C13007, and C13011).

FDA Response:
Per the eData team, excel is acceptable. However, we request that this information be provided in a .pdf file format for each study that is considered pivotal to the Agency's determination of efficacy and safety (C13006, C13007, and C13011).

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

Sponsor Response:
The sponsor requests clarification what is meant by "CRO" and "source data" in the context of the data request in Item 3(c). Further, the sponsor requests clarification that submission of information formatted in Microsoft Excel® is acceptable. Finally, the sponsor requests clarification that the scope of this request is the completed Phase 3 clinical studies (C13006, C13007, and C13011).

FDA Response:
The meaning of CRO is Contract Research Organization, which is defined further in 21 CFR 312.3(b). Source data is considered to be the initial documentation of data in a clinical study; the originator, or recorder, may document the data either on paper or electronically. In the context of 3(c) items to consider might include, for example, the following types of information: monitoring reports, correspondence between the CRO and clinical investigators, correspondence between the CRO and the sponsor, correspondence on the behalf of the sponsor to the FDA, etc.

Per the eData team, excel format is acceptable. However, we request that this information be provided in a .pdf file format for each study that is considered pivotal to the Agency's determination of efficacy and safety (C13006, C13007, and C13011).

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

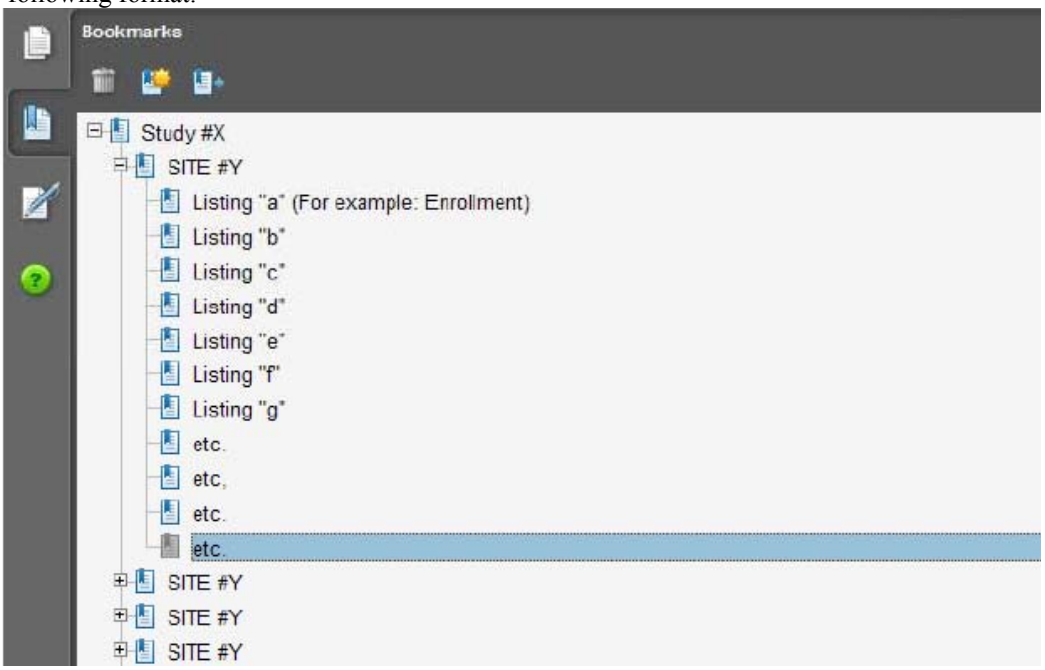
II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

Sponsor Response:
The sponsor acknowledges the request for Subject Level Data Listing by Site; however, the sponsor notes that information on screen failures, (Item 1(d))is not captured in the clinical database and therefore no information will be submitted.

FDA Response:
FDA acknowledges this limitation.

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Sponsor Response:
The sponsor proposes not to include datasets formatted in CDISC/ADaM as referenced in Part III. Does the FDA agree?

Further, the sponsor requests clarification as to whether submission of the Site Level Datasets is voluntary.

FDA Response:
Submission of the Summary Level Clinical Site Data Set is voluntary; however, when submitted it is not required to be in CDISC/ADaM format.

Attachment 1

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)

- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm

- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis

- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0 48	0 0096	0 34	0 0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0 14	0 0049	0 34	0 0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0 48	0 0108	0 33	0 0204	-1	3	2	1	0	45000 00	45000 00	Washington	George
Percent Responders	Binary	0 14	0 0049	0 33	0 0204	-1	0	2	0	3	20000 00	45000 00	Washington	George
Percent Responders	Binary	0 54	0 0092	0 35	0 0210	-1	2	2	0	1	15000 00	25000 00	Jefferson	Thomas
Percent Responders	Binary	0 19	0 0059	0 35	0 0210	-1	3	6	0	0	22000 00	25000 00	Jefferson	Thomas
Percent Responders	Binary	0 46	0 0095	0 34	0 0161	-1	4	1	0	0	0 00	0 00	Lincoln	Abraham
Percent Responders	Binary	0 12	0 0038	0 34	0 0161	-1	1	2	0	1	0 00	0 00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail com	US	Maryland	Rockville	20852	1 Rockville Pk
	555-987-6543	555-987-6540	abe@mail com	US	Maryland	Rockville	20852	1 Rockville Pk

Attachment 2

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda hhs.gov

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  Considerable discussion took place regarding the submission of the long-term safety database for vedolizumab. The Division said that a complete application must include the complete long-term safety database, which includes data from ~900 patients followed for 24 infusions, plus a 4 week follow-up as was discussed in previous meetings and relates to original requests from the Gastrointestinal Drugs Advisory Committee in the July 2011 closed meeting. Final agreement on the safety database requirements at the time of BLA submission was not reached; however, the Division expects that the BLA will be submitted when the safety database described above is available. The Division referred the Sponsor to the *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017* (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf) for further information.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

- A preliminary discussion on the need for a REMS was held and it was concluded that the Sponsor will submit a proposed REMS for the product vedolizumab with the submission of the BLA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. On November 13, 2012, a CMC-only Pre-BLA meeting was held and we agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
  - Primary Stability Lots manufactured at (b) (4) – additional stability time points of:
    - 1 lot at 30 and 36 months
    - 1 lot at 36 months
  - DP validation lots – additional stability time points for:
    - 3 lots up to and including 6 months

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  BLA NUMBER LATE COMPONENT - QUALITY

4.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

5.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

7.0 ATTACHMENTS AND HANDOUTS

Sponsor's presentation from the November 06, 2012 meeting is attached.

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
11/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 009125

MEETING MINUTES

Millennium Pharmaceuticals, Inc.
Attention: Colleen Costello, Ph.D.
Director, Regulatory Affairs
35 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN0002 (vedolizumab).

We also refer to the meetings between representatives of your firm and the FDA on July 24, 2012, and July 25, 2012. The purpose of the meeting was to discuss the clinical development plan to support registration of Vedolizumab for the treatment of ulcerative colitis and Crohn's disease.

A copy of the official minutes of the meetings is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	End of Phase 3
Meeting Date and Time:	July 24, 2012, and July 25, 2012, 3:30 p.m. to 4:30 p.m., EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 009125
Product Name:	vedolizumab
Indication:	treatment of ulcerative colitis and Crohn's disease
Sponsor/Applicant Name:	Millennium Pharmaceuticals, Inc.
Meeting Chair:	Anil Rajpal
Meeting Recorder:	Kevin Bugin

FDA ATTENDEES

Andrew Mulberg, MD, FAAP, CPI, Deputy, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joyce Korvick, MD, MPH, Safety Deputy, DGIEP
Anil Rajpal, MD, MPH, Medical Team Leader, DGIEP
Klaus Gottlieb, MD, MBA, MS, RAC, Medical Officer, DGIEP
Sushanta Chakder, PhD, Nonclinical Team Leader, DGIEP
Tamal Chakraborti, PhD, Nonclinical Reviewer, DGIEP
Kevin Bugin, MS, RAC, Regulatory Health Project Manager, DGIEP
Gerald Feldman, PhD, Quality Reviewer, Office of Biotechnology Products, Division of Monoclonal Antibodies
Mike Welch, PhD, Deputy, Office of Biometrics (OB), Division of Biostatistics III (DBIII)
LaRee Tracy, PhD, Statistics Team Leader, OB, DBIII
John Yap, PhD, Statistics Reviewer, OB, DBIII
Milton Fan, PhD, Statistics Reviewer, OB, DBIII
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology, (OCP)
Lucy Fang, PhD, Clinical Pharmacology Reviewer, OCP
Jinoo Lee, PhD, Clinical Pharmacology Reviewer, OCP

Eric Bastings, MD, Deputy, Division of Neurology Products
David Shih, MD, MS, FACPM, Team Leader, Office of Safety and Epidemiology (OSE), Office of Pharmacovigilance and Epidemiology (OPE), Division of Epidemiology 1
Christian Cao, MPAS, PA-C, Safety Evaluator, OSE, OPE, Division of Pharmacovigilance 1
Yasmin Choudhry, MD, OSE, Division of Risk Managment
Reema Mehta, MD, OSE, Division of Risk Managment
Laurie Muldowney, MD, Medical Officer, Office of Pharmaceutical Sciences

SPONSOR ATTENDEES

Millennium Pharmaceuticals Participants:

Melody Brown - Vice President, Regulatory Affairs
Colleen Costello, Ph.D.-Senior Director, Regulatory Affairs
Eric Fedyk Ph.D. - Director, Pharmacology & Toxicology
Irving Fox, M.D., CM, FRCP- Distinguished Scientific Fellow, Clinical Development
Eric Freedland M.D.- Director, Pharmacovigilance & Risk Management
Mingxiu Hu Ph.D-Senior Director, Biostatistics & Statistical Programming
Veronique Kugener, M.D., MSc, MBA - Vice President, Pharmacovigilance & Risk Management
Megan McAuliffe, ScD, MS Post-Doctoral Research Fellow, Epidemiology
Catherine Milch M.D., M.S. - Medical Director, Clinical Development
Karen Quinn, Ph.D. - Director, Regulatory Affairs
Maria Rosario, Ph.D. – Director, Clinical Pharmacology
Serap Sankoh Ph.D. - Director, Biostatistics
Veit Schmelmer, Ph. D - Senior Director, Drug Development Management
Jing Xu Ph.D. - Director, Biostatistics

Takeda Global Research and Development Participants:

Asit Parikh, M.D., PhD, Vice President General Medicine
Lesley Wise, Ph.D., Senior Director, Global PV Risk Management
Bagyashree Sundaram - Associate Director, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

Since 2008 the Division of Gastroenterology and Inborn Errors Products (DGIEP) and Millennium Pharmaceuticals, Inc (Millennium) have been having continued discussions regarding the product Vedolizumab (VZB) in development for the treatment of ulcerative colitis (UC) and Crohn's disease (CD). In this same spirit, Millennium has requested a Type C Meeting to further discuss the clinical development plan to support registration of VZB. There are four major goals of the meeting: 1) Review key clinical analyses data from the completed UC and CD phase 3 studies and obtain concurrence that there is substantial evidence of efficacy in patients with either moderately to severely active UC and CD; 2) obtain concurrence on the suitability of measuring patient exposure to VZB in terms of months as opposed to number of infusions; 3) discuss a proposed pharmacovigilance and risk management plan to be implemented post approval; 4) discuss the proposed data format for the BLA clinical and nonclinical datasets.

Two meetings were scheduled for July 24, 2012, and July 25, 2012, from 3:30 to 4:30 p.m., EDT. Preliminary comments for the meeting were sent to the Sponsor on July 21, 2012. The meetings took place as scheduled.

2.0 DISCUSSION

Clinical

Question 1: Ulcerative Colitis

The Sponsor is planning to seek approval for the use of vedolizumab for the induction and maintenance treatment of patients with moderately to severely active ulcerative colitis (UC). Specifically, the proposed claim for UC is the following:

Vedolizumab is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant of 1 or more conventional therapies including tumor necrosis factor alpha (TNFα) antagonists.

a. With respect to induction, the Sponsor believes that the highly statistically significant and clinically meaningful magnitude of treatment effect from the phase 3 Induction Study C13006 meets the criteria for substantial evidence of efficacy based on a single adequate and well-controlled trial as outlined by the Division at the End-of-Phase 2 meeting held on June 5, 2008 and the Type C meeting held on July 13, 2010.

Does the Division agree?

FDA Response:
We cannot be certain at this time that the magnitude of treatment difference that you report for your primary endpoint as well as other endpoints represents a clinically

relevant and meaningful effect size, and constitutes substantial evidence of efficacy for induction in UC. This determination can only be made after the complete efficacy data have been provided for us to review.

The requirements for demonstration of efficacy include the following:

- **statistically very persuasive findings**
- **an effect size that is clinically relevant and meaningful**
- **results that are internally consistent across multiple endpoints (involving different events)**
- **results that are internally consistent across centers (i.e., no single investigator or center provides a disproportionate favorable effect; no single center provides an unusually large fraction of patients)**
- **results that are internally consistent across subgroups and countries**

Thus, we cannot be certain at this time that the results of this single trial will necessarily constitute substantial evidence of efficacy for induction in UC.

See also Additional Comments 21, 22, and 23.

b. With respect to maintenance, the efficacy data from the phase 3 Maintenance Study C13006 are highly statistically significant and clinically meaningful and demonstrate substantial evidence of efficacy in the maintenance treatment of patients with moderately to severely active UC. The Sponsor believes that both the primary and secondary endpoints of the maintenance portion of this adequate and well-controlled study have been met with highly statistical significance and therefore, the Division's criteria for registration of vedolizumab for maintenance treatment have been met, i.e., strongly positive results and robust in a single pivotal maintenance trial and substantial evidence of efficacy for maintenance.

Does the Division agree?

<u>FDA Response:</u>
The same comments in the Response to 1a regarding demonstration of efficacy for induction in UC also apply to demonstration of efficacy for maintenance in UC.

We also note the following:

- **As we stated in the June 5, 2008 meeting[1], "If you have substantial evidence of efficacy for induction in a population, then a single adequate and well-controlled successful maintenance study in that population could be sufficient to extend the claim to maintenance in that population." Thus, it may not be possible for you to demonstrate efficacy for maintenance in UC if efficacy for induction in UC has not been demonstrated.**

[1] Response to Question 4 in the Meeting Minutes (June 5, 2008 Meeting)

- **It appears that your maintenance study was designed so that patients from two different cohorts (Cohort 1 and Cohort 2) enter into the maintenance study. We note that you have only presented the results of a combined analysis. We request that you provide a separate analysis for each of the cohorts for your primary and secondary endpoints of the maintenance study.**

See also Additional Comments 21, 22, and 23.

c. Acknowledging that a final determination of approvability will be based on the review of the totality of data in the application, the Sponsor's position is that the efficacy and safety results of the Induction and Maintenance Study C13006 support that a positive benefit risk assessment of vedolizumab in the induction and maintenance treatment of patients with moderately to severely active UC could be established.

Does the Division agree?

FDA Response:
From the efficacy perspective, there is considerable uncertainty regarding whether efficacy has been demonstrated (see Responses to 1a and 1b); however, it is possible that these uncertainties will be resolved upon the review of complete efficacy data submitted as part of the application.

From the risk assessment perspective, your proposed safety database for the BLA filing falls far short of the requirement for an adequate patient exposure that was elucidated in the September 6, 2011 Meeting.[2] See Responses to 3a and 5a.

Question 2: Crohn's Disease

The Sponsor is planning to seek approval for the use of vedolizumab for the induction and maintenance treatment of patients with moderately to severely active CD. Specifically, the proposed claim for CD is the following:

Vedolizumab is an anti-inflammatory indicated for reducing signs and symptoms, inducing and maintaining clinical remission, and eliminating corticosteroid use in patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant of 1 or more conventional therapies, or TNFα antagonists.

a. With respect to induction, the Sponsor believes that the statistically significant and clinically meaningful magnitude of treatment effect from the phase 3 Induction study C13007 in conjunction with the data from the supportive phase 3 Induction study C13011 meets the criteria to conduct two adequate and well-controlled induction studies in the population for which an indication is sought as outlined by the Division at the End-of-Phase 2 meeting held on June 5, 2008.

[2] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)

Does the Division agree?

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

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

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

We look forward to receiving the complete efficacy data for review.

See also Additional Comments 21 and 22.

Sponsors Response
See slides.

- *In C13007, two "co-primary" endpoints (amended protocol language): "The Hochberg method will be applied to control the overall Type I error rate at a 5% significant level for the multiple comparisons of the co-primary endpoints. If both p-values are ≤ 0.05, both co-primary endpoints will be declared significant. If one of the p-values for the co-primary endpoints is >0.05, the other p-value will be tested at the 0.025 level and declared significant if the p-value is ≤0.025."*
- *Study C13007, Induction, is statistically significant because the p-value for clinical remission is 0.0206 which meets the definition of significance per the original protocol and the amended protocol.*
- *Does FDA agree that study C13007 is a statistically positive study?*

Discussion:
The proposed Hochberg method does not control study-wise Type I error for the two co-primary endpoints and for the secondary endpoints. Another testing procedure, e.g., the Holms's method, would have been preferred. Since the studies are completed, this will be a review issue. The Agency will provide additional literature references on multiplicity. Regarding previous agreements and recommendations, we refer to the September 10, 2009, Type C meeting.

b. With respect to maintenance, the efficacy data from the phase 3 Maintenance Study C13007 are clinically meaningful and demonstrate substantial evidence of efficacy in the maintenance treatment of patients with moderately to severely active CD. The Sponsor's position is that the Division's criteria for registration of vedolizumab for maintenance

treatment have been met, i.e., a single successful maintenance study in CD in conjunction with substantial evidence of efficacy for maintenance.

Does the Division agree?

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

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

We also note the following:

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

See also Additional Comments 21 and 22.

c. Acknowledging that a final determination of approvability will be based on the review of the totality of data in the application, the Sponsor's position is that the efficacy and safety results of the Induction Study and Maintenance Study C13007 and the supportive Induction study, C13011, support that a positive benefit risk assessment of vedolizumab in the induction and maintenance treatment of patients with moderately to severely active CD could be established.

Does the Division agree?

FDA Response:
From the efficacy perspective, there is considerable uncertainty regarding whether efficacy has been demonstrated (see Responses to 2a and 2b).

From the risk assessment perspective, your proposed safety database for the BLA filing falls far short of the requirement for an adequate patient exposure that was elucidated in the September 6, 2011 Meeting.[4] See Responses to 3a and 5a.

[3] Response to Question 4 in the Meeting Minutes (June 5, 2008 Meeting)
[4] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)

Question 3: Pre-Marketing Safety Database

Further to FDA's comments regarding utilization of the number of infusions to evaluate the size and duration of exposure of the pre-marketing safety database as articulated at the September 6, 2011 Type C meeting, Millennium's position is that evaluation of the safety database in terms of "months of exposure" is appropriate.

a. Specifically, the comparable efficacy of vedolizumab for the Q8W and Q4W regimens, as well as the clinical pharmacological properties of vedolizumab, provide scientific support for the PML risk estimates based on the number of months of exposure to an efficacious dosing regimen rather than by the number of infusions received.

Does the Division agree?

FDA Response:
No, we do not agree.

It appears that your main rationale for measurement of exposure based on number of months (rather than number of doses) is that the two dose regimens (Q 8 weeks and Q 4 weeks) have similar efficacy, and that similar efficacy is evidence of similar pharmacologic effect.

Whether or not efficacy has been demonstrated for the Q 8 weeks and/or the Q 4 weeks regimens for each of the proposed indications will be determined during the course of review of your application. Thus, we do not agree with your rationale. As we stated in the previous meeting[5], the rationale for a minimum number of 24 infusions (rather than 24 months) is the following:

- **"…a substantial proportion of the patients in the maintenance phase of the clinical trials will be receiving Q 8 weeks treatment for approximately 1 year."**
- **"If the Q 4 weeks treatment was the approved dose, then an inadequate number of patients treated at that dose may be in the safety database at the time of BLA filing if the number is based on months of exposure rather than number of infusions."**

As we stated in the previous meeting, we request that you provide exposure data calculated using both methodologies (i.e., number of infusions and number of months). See also Additional Comment 25.

Question 4: Post Marketing Plans

[5] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)

Millennium is committed to the continued assessment of the benefit: risk profile of vedolizumab in the postmarketing setting. Millennium is developing a post-approval risk management strategy which will be described in the Biologics License Application (BLA). Millennium is seeking advice on the proposed risk management strategy. Specifically, Millennium would like to ask whether:

a. the proposals for Pharmacovigilance (PV) activities and risk minimization strategies are likely to be acceptable given the indication and setting for treatment?

FDA Response:
In the meeting package, you state that a risk assessment and minimization program has been in place since 2007 and that all patients enrolled in clinical trials have been monitored for progressive multifocal leukoencephalopathy (PML); this program includes education of health professionals and subjects participating in clinical trials on the signs and symptoms of PML, and screening of subjects at baseline and prior to each infusion via a subjective and an objective checklist. We also acknowledge provision of data from clinical trials in support of your proposed risk assessment and minimization program; these data will have to be evaluated in conjunction with the BLA submission.

You also state that the risk mitigation component of the risk minimization program will include labeling, a Medication Guide and a communication plan for prescribers and infusion centers.

Based on the information available at this time, a risk evaluation and mitigation strategy (REMS) may be necessary to ensure that the benefits of vedolizumab outweigh the risks of vedolizumab. Therefore, we encourage you to submit proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the BLA, will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act. Input from an Advisory Committee meeting, as well as additional discussion within the FDA will be necessary for us to evaluate the need for, and the elements of, a REMS.

b. the outlined proposal for the postmarketing safety study, a long-term, prospective open-label cohort study, is acceptable given the current safety profile of the product?

Does the Division agree?

FDA Response:
It is premature to comment fully at this time until further discussion at the Advisory Committee meeting, and until we have had the opportunity to fully review the BLA submission. However, an epidemiologic safety study has the potential to evaluate real-world adverse outcomes risks associated with vedolizumab use. Nevertheless, without a full study protocol including specific details of the design, methods, conduct,

and analysis, it is difficult to make a judgment on the adequacy of the study to answer the safety questions. See also Additional Comments 11 through 20.

Discussion:
Both the Agency and the Sponsor recognize the complexities related to pharmacovigilance planning and look forward to future discussions on topic.

Question 5: Regulatory

Based on the following: (i) demonstrated efficacy in patients with moderately to severely active UC or CD, (ii) the clinical safety profile of vedolizumab relative to placebo in each indication, (iii) a robust safety database at the time of filing, (iv) a robust postmarketing plan which includes a prospective cohort study to further evaluate the perceived theoretical risk of PML, and (v) a gut selective MOA based on target specificity for the a4b7 integrin, Millennium is proposing to submit an application for the registration of vedolizumab in the first quarter of 2013. Millennium's position is that the safety data available at the time of BLA submission and at the time of approval will be substantial. However, the proposed BLA submission target will be such that safety data for 1000 patients for a minimum duration of 24 months exposure at the time of an FDA AC as recommended by the Division at the September 6, 2011 Type C meeting, will not be available.

a. Millennium's position is that the substantial safety database coupled with the overall clinical benefit in the UC and CD patient populations and the proposed risk management plan in the post-marketing setting is sufficient to support the proposed BLA submission prior to obtaining the recommended safety data on 1000 patients for a minimum duration of 24 months exposure at the time of AC.

Does the Division agree?

FDA Response:
No, we do not agree with your proposed rationale; see below:

(i.) It appears that your current proposal for the safety database at the time of filing is similar to that proposed in the previous meeting (September 6, 2011) with the exception of a smaller number of patients exposed for ≥ 36 months in your new proposal. Currently, you are proposing the following numbers of patients exposed (by number of months of exposure) (data cutoff date of 6 months prior to BLA filing date): ~1300 (≥ 12 months), ~950 (≥ 18 months), ~600 (≥ 24 months), and ~100 (≥ 36 months).[6] Previously, you had proposed the following numbers of patients exposed (by number of months of exposure) (data cutoff date relative to BLA filing date not provided): 1,400 (> 12 months), 900 (> 18 months), 575 (>24 months), and 280 (> 36 months).[7]

[6] Table 3-63 on Page 167 of the Meeting Package for the July 24, 2012 and July 25, 2012 Meetings (cover letter dated June 21, 2012)
[7] Numbers of patients for the various durations calculated from Annex Figure 1 on Page 24 of the Meeting Package for the September 6, 2011 Meeting (cover letter dated August 9, 2011)

Thus, as we stated in the previous meeting[8], we disagree with your proposal from a risk assessment perspective; we believe your proposed level of exposure would be insufficient to fully assess the potential risk of PML with the proposed regimen.

Assuming there are no PML events, we continue to believe you should study at least 1,000 patients for a minimum number of 24 infusions. As we stated in the previous meeting[9], with this safety database, the 95% CI upper bound for the true PML event rate after 24 or more infusions would be 3/1000 (based on the Rule of 3) if no events are observed. With your currently proposed sample of approximately 600 patients with at least 24 months of exposure, the upper bound is increased to 5 per 1000, which is unacceptably high to sufficiently rule out potential risk in the intended population.

In addition, as we stated in the previous meeting, a substantial proportion of the patients that have received ≥ 24 infusions should have received ≥ 36 infusions.[10] We note that in your new proposal, the number of patients that will have been exposed for ≥ 36 months (~100) appears to be lower than that proposed previously.

Our current thinking based on the information you have provided in the meeting package is that the efficacy data does not justify a smaller safety database than that we elucidated in the September 6, 2011 Meeting. See Responses to Questions 1 and 2.

Sponsor's Response:

- *Millennium is committed to studying 1000 pts for a minimum duration of 24 infusions*
  - *Protocol amendment in March 2012 (s/n 0428) to add 400 pts to the open label C13008 long term safety study*
  - *Enrollment projected to complete prior to December 2012*
  - *Safety read-out on 1000 pts with a minimum duration of exposure of 24 infusions projected to be Nov 2013 timeframe (or July/August 2014 by months)*
- *The efficacy demonstrated in UC patients is unprecedented.*
  - *Closest therapy with similar effect size relative to placebo is infliximab in the naïve only population (ACT1 and ACT2)*
- *The efficacy demonstrated in Crohn's Disease meets an urgent clinical need in patients with few or no treatment alternatives.*

Discussion:

When considering the cut-offs for the safety database, we remind you that the goal is to provide sufficient data for the advisors to review.

[8] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)
[9] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)
[10] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)

The Agency stated that data from at least 900 patients that received ≥ 24 infusions (with a minimum of 4 weeks of follow-up after the last infusion) would be required for us to conduct a review and present to an Advisory Committee. The Agency added that if the Sponsor submits the BLA early (i.e., does not reach this level of exposure by the time of the 120-day safety update report with a reasonable data cutoff date), then it is possible that the additional exposure data could be submitted after the 120-day safety update report, but would most likely be considered a major amendment that would result in a 3-month extension. The Agency noted that the timing of the Advisory Committee would need to occur relative to the time that the Agency receives adequate exposure data for review.

The Agency reminded the sponsor that it would be preferable to have data from 1000 patients for ≥ 24 infusions as stated earlier. The Agency also reminded the sponsor that a substantial proportion of patients should have received ≥ 36 infusions.

The Agency noted that the numbers of patients should be actual (not projected) numbers. The Agency also requested that the sponsor provide tables of exposure data as described in Additional Comments 25 and 26 at the next meeting that is planned (the Pre-BLA meeting) and with the BLA submission.

During the submission review, it would be expected that you submit monthly updates of exposure data, see Additional Comments 25 and 26.

<u>Follow-up discussion from yesterday about Anti-JCV Antibody Testing:</u>

The Agency stated that this is an informed consent issue. Patients should be made aware that there are similarities in mechanism of action between your product and Tysabri, and that there is a higher risk of PML in Tysabri-treated patients who were anti-JCV antibody positive. (See emails dated July 3 and July 12, 2012.) The Agency noted that this request was also made for other integrin antagonist products in development.

The Agency also noted that an anti-JCV antibody assay is not currently commercially available for any of the integrin antagonist products (other than Tysabri), and that the Division is working with CDRH to determine the regulatory pathway for use of an anti-JCV antibody assay in ongoing clinical trials of these products.

We will discuss this further once a pathway for utilizing the assay is available.

(ii.) It appears that you are also proposing that additional patient exposure in the interval from filing to the planned AC meeting (data cutoff of one month before the AC meeting) should count towards the requirement for an adequate patient exposure at the time of BLA filing. This proposal is not acceptable for the following reasons:

- **It appears that the number of patients that will have been exposed to ≥ 24 infusions will be considerably less than 1,000.**

- **Even if the numbers of patients exposed (for the various minimum durations and minimum number of infusions) were acceptable, the proposed data cutoff of one month before the AC meeting would not allow sufficient time for you to perform adequate adjudications of possible cases of PML, and to perform adequate evaluations of other adverse events; there would be little or no time remaining within this one month window for the Division to evaluate the safety data.**

If your safety database at the time of BLA filing (with a reasonable data cutoff date) is less than 1000 patients exposed to ≥ 24 infusions (with a substantial proportion of these patients exposed to ≥ 36 infusions), it would be acceptable for additional data to be submitted as part of the Day 120 Safety Update Report (again, with a reasonable data cutoff date) to count towards the requirement of an adequate safety database at the time of BLA filing.

(iii.) We note the following regarding methods of calculating exposure:

- **In Table 3-63 of the current meeting package, you state that the number of patients that will have received ≥ 24 months of treatment at the proposed time of filing the BLA (January 2013) (data cutoff date of July 2012) is ~600. However, this number appears to be calculated with the addition of 8 weeks of treatment to each patient (to account for the persistence of vedolizumab in the circulation). We are concerned that the number of patients that will have received ≥ 24 months of treatment at the proposed time of filing the BLA (January 2013) (data cutoff date of July 2012) will be substantially lower than ~600; the number of patients that received ≥ 24 infusions will be even smaller because of the substantial proportion of patients that received Q 8 week treatment in the maintenance trials for 1 year.**

- **In Table 4-3 of the current meeting package, you state that the number of patients that will have received ≥ 24 infusions at the proposed time of filing the BLA (January 2013) (data cutoff date of January 2013) is ~600, and this number is calculated without the addition of 8 weeks of treatment to each patient; however, the cutoff date may not be feasible as it is the same month that you propose to file the BLA. We are concerned that the number of patients that will have received ≥ 24 infusions at the proposed time of filing the BLA (January 2013) (data cutoff date of July 2012) will be substantially lower than ~600.**

We look forward to seeing the exposure data calculated without additional time or infusions added (to account for the persistence of vedolizumab in the circulation), with a reasonable cutoff date (e.g., 6 months before the proposed

time of BLA filing), and using both methodologies (i.e., number of infusions and number of months) (see Additional Comment 25).

(iv.) As we noted in the previous meeting[11], we anticipate that the risk of PML is increased in patients with a history of immunosuppressant use and/or patients that are receiving concomitant immunosuppressants. We request that you also provide exposure data by categories of prior and concomitant immunosuppressant use (see Additional Comment 26).

b. Millennium's position is that the benefit of vedolizumab outweighs the identified and potential safety risks as supported by the substantial safety database coupled with the overall clinical benefit in the UC and CD patient populations. The proposed risk management plan in the post-marketing setting, and that the targeted and selective MOA of vedolizumab support that no additional elements would be required and no restrictions related to the perceived theoretical risk of PML will be required by FDA to be included in the product labeling.

Does the Division Agree?

FDA Response:
It is premature to answer this question. See also the Response to Question 4a.

Question 6: Nonclinical Data

For the planned vedolizumab BLA, Millennium proposes to provide nonclinical data for all toxicology and safety pharmacology studies conducted as appendices to the study reports in Adobe PDF format. Millennium does not plan to submit nonclinical datasets in analyzable format, such as SAS or SDTM.

Does the Division agree with this approach?

FDA Response:
Yes. We agree.

Question 7: Case Report Tabulation

Millennium is planning to submit Case Report Tabulation (CRT) as part of the BLA package. The CRT will include documentation of data (define.xml) and Study Data Tabulation Model (SDTM) for all clinical studies: L297-005, L297-006, L297-007, L299- 016, M200-021, M200-022, C13001, C13002, C13004, C13005, C13006, C13007, C13008, C13009, C13010, C13011, C13012, and C13013. In addition, we plan to submit Analysis Data published in SDS 1.6 format

[11] Response to Question 1 in the Meeting Minutes (September 6, 2011 Meeting)

along with Source Data published in SDS 1.6 format. Does the Division agree with this approach?

FDA Response:
The Division will consult with the eData support team and provide you with feedback at a later time. We also recommend sending this question to edata@fda.hhs.gov.

ADDITIONAL FDA COMMENTS:

Clinical Pharmacology:
We have the following general Clinical Pharmacology comments in the absence of information on clinical pharmacology studies in your briefing package:

8. **Provide adequate clinical pharmacology data to justify the proposed dosing regimen for labeling.**

9. **Evaluate the impact of immunogenicity of your product on pharmacokinetics/pharmacodynamics, efficacy, and safety of your product. Submit the analysis datasets.**

10. **If you intend to submit model-based population analyses (i.e., modeling and simulation) in the clinical pharmacology section, submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:**
    - **All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
    - **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).**

Epidemiology/Safety Statistics:
Specific recommendations for the future postmarketing observational study protocol submission are provided below. These recommendations are subject to change based on the Advisory Committee meeting, the development program outcome, and further internal FDA discussion.

11. **Clearly state the primary and secondary objectives. If the study's main purpose is to evaluate the risk of PML in vedolizumab users, word the objectives accordingly.**

12. **Specify outcomes, and develop case definitions.**

13. **Design the study around a stated, testable hypothesis to rule out a certain level of risk with a specific amount of precision based on a primary endpoint of interest (e.g. PML risk after 24 infusions, etc.). This will ensure that the final study results are interpretable and meaningful.**

14. **Recalculate sample size based on ruling out the lower bound of natalizumab-associated PML risk (not the point estimate) or based on the lowest-risk outcome (such as PML in exposures shorter than 24 months and non-PML outcomes).**

15. **Consider longer follow-up times for cancer outcomes.**

16. **Include only new users of vedolizumab to avoid depletion-of-susceptibles or prevalent user bias.**

17. **Consider a control group for non-PML outcomes.**

18. **Please do not omit the appendix on retention strategies.**

19. **Describe methods to minimize loss to follow-up and to follow subjects who stop vedolizumab therapy.**

20. **Describe the recruitment methods that are likely to achieve the desired enrollment.**

Clinical/Statistics:

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

22. **The Division of Gastroenterology and Inborn Errors Products (DGIEP) is currently re-evaluating endpoint definitions in CD and UC. DGIEP is also currently re-evaluating the requirements to support labeling claims for "mucosal healing" in UC (i.e., definition, standardized endoscopy methodology, use of histology, etc.). This process includes internal discussions as well as workshops that include external experts; FDA is currently planning an Inflammatory Bowel Disease (IBD) Workshop in Fall 2012 in which many of these topics are likely to be discussed.**

Sponsor Response:

- *Please provide clarification of topics to be discussed.*
- *Do you foresee any impact to this submission?*

Discussion:
The Agency stated that the adult IBD portion of the Workshop will focus on Ulcerative Colitis endpoints. The Workshop is not intended to be an advisory meeting, so the discussions in the Workshop are not expected to have a direct impact on this submission.

23. We note that clinical remission is defined as total Mayo score of ≤ 2 and no individual sub score > 1 in Study C13006. We request that you also conduct analyses using the following alternate definition of clinical remission: total Mayo score of ≤ 2 and no individual subscore > 1 where the Rectal Bleeding subscore must equal 0 and the Endoscopy subscore must equal 0.

24. In Table 3-42 of the meeting package, you have provided results from Study C13011 for the primary endpoint and four secondary endpoints in the ITT population, and in the TNFα antagonist failure subgroup. We request that you also provide all these results in the TNFα antagonist naïve subgroup.

25. Provide exposure data calculated using both methodologies (i.e., number of infusions and number of months) as described in the Responses to Questions 3a and 5a to produce tables like the ones below.

a. Exposure Data Calculated Using Number of Infusions

Table 1. Exposure Data Calculated Using Number of Infusions

Number of Infusions	Number of Patients* (Cutoff Date#)
≥ 6 Infusions	a
≥ 12 Infusions	b
≥ 18 Infusions	c
≥ 24 Infusions	d
≥ 36 Infusions	e
≥ 48 Infusions	f

* Provide the number of patients corresponding to each category of number of infusions (without any additional infusions added to account for the persistence of vedolizumab in the circulation).
# Propose a reasonable cutoff date (e.g., six months before the time of submission of the BLA).

b. Exposure Data Calculated Using Number of Months

Table 2. Exposure Data Calculated Using Number of Months

Number of Months	Number of Patients* (Cutoff Date#)
≥ 6 Months	g
≥ 12 Months	h
≥ 18 Months	i
≥ 24 Months	j
≥ 36 Months	k
≥ 48 Months	l

* Provide the number of patients corresponding to each category of number of months (without any additional time added to account for the persistence of vedolizumab in the circulation).
#Propose a reasonable cutoff date (e.g., six months before the time of submission of the BLA).

26. Provide exposure data by categories of prior and concomitant immunosuppressant use as described in the Response to Question 5a (part iv.) to produce tables like the ones below.

a. Exposure Data by Prior and Concomitant Immunosuppressant Use Categories Calculated Using Number of Infusions

Table 3. Exposure Data by Prior and Concomitant Immunosuppressant Use Categories Calculated Using Number of Infusions

Category	# Vedolizumab Infusions*,#					
	≥ 6	≥ 12	≥ 18	≥ 24	≥ 36	≥ 48
Prior Immunosuppressant Use						
Yes	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
No	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Immunosuppressant Use						
Yes	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
No	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

* Provide the number of patients corresponding to each category of number of infusions (without any additional infusions added to account for the persistence of vedolizumab in the circulation).
#Propose a reasonable cutoff date (e.g., six months before the time of submission of the BLA).

b. Exposure Data by Prior and Concomitant Immunosuppressant Use Categories Calculated Using Number of Months

Table 4. Exposure Data by Prior and Concomitant Immunosuppressant Use Categories Calculated Using Number of Months

Category	# Months of Vedolizumab Treatment*,#					
	≥ 6	≥ 12	≥ 18	≥ 24	≥ 36	≥ 48
Prior Immunosuppressant Use						
Yes	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
No	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Concomitant Immunosuppressant Use						
Yes	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
No	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

* Provide the number of patients corresponding to each category of number of months (without any additional time added to account for the persistence of vedolizumab in the circulation).
#Propose a reasonable cutoff date (e.g., six months before the time of submission of the BLA).

3.0 ATTACHMENTS AND HANDOUTS

Millennium Pharmaceuticals Inc Slide Presentations

31 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
08/08/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 9125

Millennium Pharmaceuticals, Inc.
Attention: Colleen Costello, Ph.D.
Director, Regulatory Affairs
35 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MLN0002.

We also refer to the telecon between representatives of your firm and the FDA on September 26, 2008. The telecon consisted of a presentation of the slides sent by Millennium as well as detailed discussions in which clinical questions and issues were addressed.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

At the end of the telecon, there was an unresolved issue for which it was agreed that we would provide an additional response or have additional dialogue with you. The issue was the acceptability of your proposal to allow concomitant immunosuppressant use for up to six weeks (in the proposed placebo-controlled Phase 3 induction studies in CD and in UC) but to otherwise prohibit concomitant immunosuppressant use throughout the Phase 3 studies.

After further consideration and internal discussions, we have the following comment on this issue:

- We now agree that it will be acceptable to allow concomitant immunosuppressant use for up to six weeks (in the proposed placebo-controlled Phase 3 induction study in UC [Induction Cohort 1 of Study C13006] and in the proposed placebo-controlled Phase 3 induction study in CD [Induction Cohort 1 of Study C13007]), provided that concomitant immunosuppressant use will otherwise be prohibited throughout the Phase 3 studies. We are basing this decision on your agreement to modify your proposed selection criteria for prior use of conventional therapies so that patients enrolled must meet the stricter requirement of inadequate response or intolerance to immunosuppressants or TNFα antagonists, rather than

the previously proposed requirement of inadequate response or intolerance to either corticosteroids, immunosuppressants, or TNFα antagonists.

If you have any questions, contact Roland Girardet, Regulatory Project Manager at (301) 796-3827.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products

Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type C
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 26, 2008 3:00-4:00 pm
Meeting Location:	Teleconference (CDER WO Bldg.22)
Application Number:	IND 9125
Product Name:	MLN0002
Received Briefing Package	August 4, 2008
Sponsor Name:	Millennium Pharmaceuticals, Inc.
Meeting Requestor:	Colleen Costello
Meeting Chair:	Dr. John Hyde
Meeting Recorder:	Frances Fahnbulleh
Meeting Attendees:	

FDA Attendees:

Anne Pariser, M.D., Acting Deputy Director, Division of Gastroenterology Products (DGP)
John Hyde, Ph.D., M.D., Medical Team Leader, DGP
Anil Rajpal, M.D., Medical Reviewer, DGP
Eric Bastings, M.D., Medical Team Leader, Division of Neurology Products
Thomas Moreno, M.S., Regulatory Health Project Manager, DGP
Frances Fahnbulleh, Pharm.D., Regulatory Health Project Manager, DGP
Jang-Ik Lee, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology

External Constituent Attendees:

Melody Brown, B.S., Vice President, Worldwide Regulatory Affairs
Colleen Costello, Ph.D., Director, Worldwide Regulatory Affairs
Irving Fox, M.D., C.M., FRCP, Distinguished Scientific Fellow, and Head of Inflammation Clinical Research
Catherine Milch, M.D., Associate Medical Director, Clinical Research
Lisa von Moltke, M.D., FCP, Senior Director Clinical Pharmacology
Asit Parikh, M.D, Ph.D., Associate Medical Director, Clinical Research
Veit Schmelmer, Ph.D., Senior Director, Development Project Management
Catherine Scholz, Pharm.D., Associate Director, Clinical Pharmacology
Nancy Simonian, M.D., Chief Medical Officer
Mingxiu Hu, Ph.D., Director, Biostatistics

(b) (4)

BACKGROUND:

MLN0002 is a humanized antibody specific to the human α4β7 integrin expressed on lymphocytes. MLN0002 is being investigated for the treatment of ulcerative colitis (UC) and Crohn's disease (CD).

MEETING OBJECTIVES:
Millennium was granted a Type C meeting (telecon) to address three outstanding action items from the Type B meeting held on June 5, 2008. Specifically, these items were: (1) Millennium's proposal for JC viremia testing and monitoring; (2) Millennium's proposal for the use of concomitant immunosuppressive therapies during the Phase 3 trials; and (3) FDA's request for a comprehensive PK and PD package which addresses clinical pharmacology issues.

DISCUSSION:
The FDA responded with preliminary responses on September 25, 2008, to the questions submitted by Millennium Pharmaceuticals, Inc. The following meeting minutes contain each sponsor question, the FDA preliminary responses in boldface, and key points from the meeting discussion on September 26, 2008, in bold italics. Millennium presented a slide deck that is appended to these minutes.

List of Specific Questions, Grouped by Discipline

Clinical

Question 1:
As a follow-up to the clinical End of Phase 2 meeting held on 05 June 2008, separate letters from Dr. Eugene Major and Dr. Joseph Berger will be provided that discuss the frequency of persistent viremia in healthy subjects and in patients treated with integrin antagonists.

In addition, the rationale is provided for Millennium's proposal to batch test for JC viremia every 2 months and regularly analyze the data for any relationship between MLN0002 exposure and JC viremia.

Does the Division agree with Millennium's proposed testing and monitoring plan for JC viremia in the phase 3 trials?

FDA RESPONSE TO QUESTION 1:
Yes, we agree.

Discussion at Meeting:
There was no further discussion during the meeting.

Question 2:
In accordance with the Division's request as a follow-up to the clinical End of Phase 2 meeting held on 05 June 2008, a documentation package is being submitted to the IND describing how restricting concomitant medications during the phase 3 placebo-controlled trial will prevent the

successful execution of a placebo-controlled maintenance trial with the key endpoints necessary to support a maintenance indication.

Based on the implications outlined in the Company Position Statement in Question 3 of the Briefing Book for Type B Meeting (Clinical End of Phase 2; IND 9,125 Serial No. 0072), Millennium has presented an appropriate proposal concerning the use of corticosteroids and immunomodulators, both of which comprise standard of care therapies for IBD in the MLN0002 Phase 3 studies.

Millennium's position statement allows for the use of corticosteroids and immunomodulators with explicit limitations on dose and duration of therapy, and mandated corticosteroid tapering. This proposal permits risk minimization without compromising the endpoints of the placebo-controlled studies or denying access to standard of care medications in the placebo-treated population, and therefore should be implemented.

Does the Division agree?

FDA RESPONSE TO QUESTION 2:

Steroid Taper: We accept your proposal to start tapering steroids at Week 6 (in Studies C13006 and C13007) and at Week 8 (in Study C13008) in patients that are in clinical response, or to start tapering steroids at the subsequent visit when clinical response is achieved.

Concomitant Steroids: We accept your proposal to allow concomitant steroid use for up to one and one-half years given the protocol provisions to limit steroid dose and to mandate tapering of steroids.

Concomitant Immunosuppressants: Given the current state of knowledge about MLN0002, we do not accept your proposal to allow concomitant immunosuppressant use for up to one year; there is reasonable concern that the risk of PML is increased with concomitant immunosuppressant use. At this stage in the development of your product, we therefore continue to request that you prohibit concurrent use of immunosuppressants and MLN0002. (See below for study design options that may make this requirement more feasible.)

Prior Immunosuppressants: Given the current state of knowledge about MLN0002, we remain concerned about the risk of recent immunosuppressant use. At this stage in the development of your product, we therefore continue to request that you propose a washout period as tolerated for prior immunosuppressants in order to minimize prior exposure to immunosuppressants.

Enrollment Criteria Based on Prior Therapies: We request that you modify your proposed selection criteria for prior use of conventional therapies so that a population is selected for which the risk is more acceptable; we request that you modify the selection criteria so that patients enrolled must meet the stricter requirement of inadequate response or intolerance to immunosuppressants or TNFα antagonists rather than the currently proposed

requirement of inadequate response or intolerance to either corticosteroids, immuno-suppressants, or TNFα antagonists. This request is based on internal discussions since the June 2008 meeting.

<u>Study Design Options</u>: We request that you modify the design of each of your proposed induction and maintenance studies so that concurrent immunosuppressant and MLN0002 use is prohibited. (We have provided a set of options below.) Option #1 is the current study design with no concomitant immunosuppressants allowed. The new options are Options #2, #3, and #4; these are aimed at addressing your concerns about allowing access to standard of care therapies and about not confounding analyses of study endpoints, while prohibiting concurrent immunosuppressant and MLN0002 use. In the new options, no patient is required to stop standard of care therapy and accept placebo; this addresses the concern of leaving control arm patients untreated. Each control arm patient will receive standard of care therapy (Option #2) or approved therapy (Options #3 and #4).

<u>Option #1</u>: Placebo-controlled studies

- **With the revised enrollment criteria based on prior therapies, a higher proportion of patients will be enrolled that are true failures of immunosuppressants, and are not currently being treated with immunosuppressants. Thus, it may be more feasible to conduct a placebo-controlled study while prohibiting concomitant immuno-suppressants.**

<u>Option #2</u>: Superiority studies (Immunosuppressant as control)

- **<u>Prior Immunosuppressant Therapy</u>: Patients that had inadequate response to, lost response to, or were intolerant of prior immunosuppressants should be enrolled if they have a reasonable expectation of benefit from the control treatment. For example, patients that are partly controlled on immunosuppressant therapy should continue on that therapy as the control treatment. (See also FDA Additional Clinical Comment 2b.)**

<u>Option #3</u>: Superiority studies (TNFα antagonist as control)

- **<u>Prior TNFα Antagonist Therapy</u>: Patients that had inadequate response to, lost response to, or were intolerant of prior TNFα antagonist therapy should be enrolled if they have a reasonable expectation of benefit from the control treatment. For example, patients that are partly controlled on TNFα antagonist therapy should continue on that therapy as the control treatment. (See also FDA Additional Clinical Comment 2b.)**

<u>Option #4</u>: Non-inferiority studies (TNFα antagonist as control)

- **<u>Prior TNFα Antagonist Therapy</u>: same as that for Option #3**
- **<u>Non-Inferiority Trial Design Features</u>: Important details of the non-inferiority (NI) trial design must adhere closely to the design of the placebo-controlled trials for which historical sensitivity to the drug's effects has been determined. For example, the entry criteria and primary endpoint should be nearly the same between the proposed NI study and the previous placebo-controlled studies, and you should discuss your rationale and justification for differences. (See also discussion below.)**

A challenge of the NI trial option (Option #4) is that the requirement to enroll patients that had inadequate response or intolerance to prior immunosuppressants or TNFα antagonists may conflict with the requirement for NI trials to have entry criteria that are nearly the same as that of the previous placebo-controlled trials for which historical sensitivity to the drug's effects has been determined.

Discussion at Meeting:
Millennium stated that the Division's current request to modify the enrollment criteria appears to contradict the meeting minutes from June 5, 2008, in which the Division indicated that it would be acceptable to enroll patients who have failed at least one conventional therapy, where conventional therapy is defined as steroids, immunomodulators, and TNFα antagonists (see Slides 3 to 4). Further, Millennium reiterated their rationale for the patient population that they initially proposed (see Slide 5). Millennium pointed out that the Division's currently proposed population would, in effect, be a TNFα antagonist failure population, because very few patients who have failed immunosuppressants will enroll in a placebo-controlled trial; most will be tried on a TNFα antagonist first. Millennium stated that limiting enrollment to such a study population will make development in CD and UC very challenging. Millennium requested further clarification, and requested the Division to reconsider this enrollment criteria request.

The Division explained that the request to modify the enrollment criteria is based on internal discussions since the June 5 meeting; the goal of this modification is to select a population for which the risk may be more acceptable. The Division added that the development of a drug that is in a class that is currently under restricted distribution poses a difficult development path; thus, a stepwise development plan may be the most appropriate for MLN0002.

Millennium stated that they do not believe that MLN0002 is in the same class as Tysabri and that they will proceed with their current enrollment criteria in studies outside of the United States. Therefore, a future BLA would consist of different study populations inside versus outside the United States.

Millennium presented Slides 6 to 9 to support their assertion that concurrent use of immunosuppressants and MLN0002 does not pose a safety concern. To address the Division's concerns about concomitant immunosuppressant use, Millennium asked the Division to consider a revised proposal that would allow patients to continue on concomitant immunosuppresants for six weeks into the trial (see Slide 10). Millennium pointed out that each of the cases of PML with Tysabri occurred after a long duration of treatment; no PML cases occurred after only six weeks of Tysabri use. Millennium's rationale for the revised proposal also included the following key points: (1) Current safety data with concomitant medications supports the proposal; (2) Patient's and Investigator's concerns about stopping existing therapy prior to initiation of study drug will be addressed; (3) The potential effect on the primary endpoint at six weeks will be minimized; (4) Management of immunomodulator discontinuation during the clinical trial will be made more feasible; and (5) Based on expert advice, the technical impact on the maintenance study is acceptable. Millennium concluded that they believe that their revised proposal will ensure safety while allowing adequate patient enrollment.

FDA agreed to consider the proposal internally, and noted that the Division Director's concurrence would be required. FDA advised Millennium to follow up with the Division in about two weeks to find out if a decision had been made.

Question 3:
As a follow-up to the clinical End of Phase 2 meeting held on 05 June 2008, the Division requested that Millennium submit a comprehensive package of pharmacokinetic (PK) and pharmacodynamic (PD) information to address the following clinical pharmacology issues as documented in the draft meeting minutes:

- the human anti-human antibody (HAHA) status of subject data used in the estimation of target concentration
- the number of subjects included in the estimation of target concentration
- the exclusion of HAHA positive subject data from the population PK modeling used in the simulation of peak/trough concentration for the proposed regimens.

It is Millennium's position that the information provided during the End of Phase 2 meeting on 05 June 2008, in conjunction with the information contained in the Briefing Book for that meeting (Clinical End of Phase 2; IND 9,125 Serial No. 0072, section 5.3.3, Summary of Clinical Pharmacology), has provided sufficient clarification and addresses the Division's request for a comprehensive PK and PD package.
Does the Division agree?

FDA RESPONSE TO QUESTION 3:
No. We do not agree.
The previous meeting package appeared to be a selective summary of PK and PD information rather than a comprehensive package. As a result, FDA could not adequately evaluate your population PK modeling approach prior to the meeting. Although you provided some additional information during the meeting such as the number of subjects included in the analysis, such limited and impromptu information was not sufficient to give you adequate comments and recommendations without sufficient preparation and internal discussion.

Discussion at Meeting:
There was no further discussion during the meeting.

FDA ADDITIONAL CLINICAL COMMENTS:

1. **It is not known with certainty that excluding patients that have leukocyte or specific leukocyte subset counts below pre-specified limits at screening and during the course of the study will reduce the risk of PML and other opportunistic infections. However, these provisions provide some assurance that patients in the study are immuno-competent, and thus may increase the safety of the study.**

   At screening, you have proposed excluding patients if they have WBC < 3 X 10^9/L or lymphocyte count < 0.5 X 10^9/L. Please provide for the Division's review your rationale including supporting data for: (1) the proposed cutoff values; and (2) selection

of overall WBC count and lymphocyte count for screening, rather than other leukocyte subsets (e.g., neutrophil count).

During the course of the study, you have proposed that lymphocyte counts will be monitored. If the absolute lymphocyte count falls below the cutoff of 500 X 10^9/L, then immunosuppressants will be stopped; if the absolute lymphocyte count persistently falls below 500 X 10^9/L, then MLN0002 will be stopped. It appears that you have erroneously written 500 X 10^9/L instead of 0.5 X 10^9/L in the draft protocols that were submitted in the meeting package for the June 5, 2008 meeting; please clarify whether or not this is an error, and make any necessary corrections to the proposed protocols. Please provide for the Division's review your rationale including supporting data for: (a) the proposed cutoff value for lymphocyte count; and (b) selection of lymphocyte count for monitoring, rather than overall WBC count or other leukocyte subsets (e.g., neutrophil count).

Discussion at Meeting:
Millennium acknowledged that there was an error in the draft protocols with regard to lymphocyte count cutoff which should read 0.5 X 10^9/L instead of 500 X 10^9/L. Millennium further noted that the lymphocyte count cutoff of 0.5 X 10^9/L is the same cutoff that was used in previous MLN0002 studies.

Regarding the baseline total WBC count and lymphocyte exclusions, Millennium noted that there are no universal criteria; however, the cutoffs chosen are consistent with clinical practice. Millennium added that they believe that these criteria will provide reasonable assurance of host resistance (see Slide 12).

Regarding the on study lymphocyte monitoring criteria, Millennium noted that the cutoff threshold corresponds to the Grade 2 severity in Division of AIDS Adverse Event Grading. Millennium added that the CD patient who developed PML on natalizumab was described as lymphopenic.

FDA asked if neutrophil count was considered for either entry or monitoring. Millennium responded that neutrophils are not a target of the drug, but that patients with low neutrophil counts will be excluded at entry.

FDA asked if overall WBC count was considered for monitoring. Millennium responded that overall WBC count monitoring is not believed to be as valuable as lymphocyte monitoring.

2. **We remind you that recommendations from the June 5, 2008 meeting still apply. We have reiterated two of those recommendations below because of their pertinence to today's discussion.**

   a. **We recommended that you conduct an additional adequate and well-controlled induction study for each of the disease populations (e.g., UC and CD). (See also**

FDA Responses and Discussion at Meeting for Questions 4, 5, and 6 from the June 5, 2008 Meeting.)

b. We recommended that you tailor criteria for "failure" (had inadequate response, lost response, or was intolerant) to each specific agent (e.g., steroids, immuno-suppressants, or TNFα antagonists), and specify the dose and duration of that agent that must be tried to be considered an adequate trial. For stating that the population consists of "failures" of one or more of these agents in the indication statement of the labeling, we recommended that you develop criteria and collect data that provide adequate documentation to support that characterization of the patient population. (See also FDA Responses and Discussion at Meeting for Question 3a from the June 5, 2008 Meeting.)

Discussion at Meeting:
There was no further discussion during the meeting.

Attachment:
Millennium Slide Handout

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Linked Applications	Sponsor Name	Drug Name
IND 9125	MILLENNIUM PHARMACEUTICALS INC	Humanized Monoclonal Antibody (LDP-02) to Alpha 4 Beta 7 Integrin

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/s/

DONNA J GRIEBEL
10/24/2008

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476/0
BLA 125507/0

LATE-CYCLE MEETING MINUTES

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Entyvio (vedolizumab).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 26, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kevin Bugin, Senior Regulatory Project Manager at (301) 796-2302

Sincerely,

{See appended electronic signature page}

Anil Rajpal, M.D., M.P.H.
Medical Team Leader
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Research and Evaluation

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 26, 2013, from 10:30 AM to 12:00 PM
Meeting Location: White Oak Building 02, Conference Room 2045
10903 New Hampshire Ave,
Silver Spring, MD 20903

Application Number: BLA 125476/0 & BLA 125507/0
Product Name: Entyvio (vedolizumab)
Indication: ulcerative colitis and Crohn's disease
Applicant Name: Takeda Pharmaceuticals U.S.A., Inc.

Meeting Chair: Anil Rajpal
Meeting Recorder: Kevin Bugin

FDA ATTENDEES

Office of New Drugs
John Jenkins, MD, Director

Office of Drug Evaluation III
Julie Beitz, MD, Director
Amy Egan, MD, Acting Deputy

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, MD, Director
Joyce Korvick, MD, MPH, Deputy for Safety
Anil Rajpal, MD, MPH, Clinical Team Leader
Laurie Muldowney, MD, Clinical Reviewer
Klaus Gottlieb, MD, MBA, RAC, Clinical Reviewer
Sushanta Chakder, PhD, Nonclinical Team Leader
Tamal Chakraborti, PhD, Nonclinical Reviewer
Kevin Bugin, MS, RAC, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Pharmacometrics
Yow-Ming Wang, PhD, Team Leader
Lanyan (Lucy) Fang, PhD, Clinical Pharmacology Reviewer
Nitin Mehrotra, PhD, Team Leader
Justin Earp, PhD, Clinical Pharmacometrics Reviewer

Office of Biotechnology Products/Division of Monoclonal Antibodies
Sarah Kennett, PhD, Branch Chief

Rashmi Rawat, PhD, Team Leader
Qing (Joanna) Zhou, PhD, Reviewer

Office of Biotechnology Products/Biotechnology Assessment Branch
Patricia Hughes, PhD, Team Leader
Steve Fong, PhD, Reviewer, Drug Product
Reyes Candauchacon, PhD, Reviewer, Drug Substance

Office of Biostatistics/Division of Biometrics III
Freda Cooner, PhD, Acting Team Leader
Milton Fan, PhD, Reviewer

Office of Biostatistics/Division of Biometrics VII
Clara Kim, PhD, Team Leader
John Yap, PhD, Reviewer

Office of Safety and Epidemiology/Division of Risk Management
Kendra Worthy, PharmD, Team Leader
George Neyarapally, PharmD, Reviewer

Office of Safety and Epidemiology/Division of Pharmacoviligance
Christian Cao, MD, Safety Evaluator

Office of Program & Strategic Analysis;
Kimberly Taylor, Operations Research Analyst

Eastern Research Group
(b) (6), Independent Assessor of PDUFA V

APPLICANT ATTENDEES
Brihad Abhyankar, FRCS, MBA, Senior Medical Director, Clinical Science
Eva Barbarics, PhD, Senior Scientist II, Analytical Development, Biologics
Melody Brown, Vice President, Head of Global Regulatory Affairs, Oncology/Immunology/Respiratory
Collen Costello, PhD, Snior Director, Global Regulatory Affairs
Willow DiLuzio, PhD, Associate Director, Biologic Formulations
Eric Fedyk, PhD, Senior Direcvtor, Therapetuic Area Strategy, Immunology and Respiratory
Thomas Harris, Global Regulatory Head, Global Regulatory Affairs
Mingxiu Hu, PhD, ASA Fellow, Vice President, Head of Global Biostatistics
Vivek Kadambi, PhD, Vice President, Global Pharmacovigilance
Catherine Milch, MD, MS, Senior Director, Clinical Research
Asit Parikh, MD, PhD, Vice President Gastroenterology and General Medicines R & D
Karen Quinn, PhD, Senior Director Global Regulatory Affairs, CMC
Maria Rosario, PhD, Director, Clinical Pharmacology

Serap Sankoh, PhD, Director, Biostatistics
Veit Schmelmer,PhD, Senior Director, Drug Development Management
Norbert Schuelke, PhD, Director Biologics Process Development
Jesse Shick, MD, Medical Director, Pharmacovigilance
Elizabeth Spinella Izbicki, Director, Commercial Quality
Bagyashree Sundaram, MS, Director Global Regulatory Affairs
Lesley Wise, PhD, Vice President, Global Pharmacovigilance Risk Management and Pharmacoepidemiology
Jing Xu, PhD, Senior Scientific Fellow, Biostatistics

1.0 BACKGROUND

BLA 125476/0 and BLA 125507/0 were submitted on June 20, 2013, for Entyvio (vedolizumab).

Proposed indication(s): ulcerative colitis & Crohn's disease

PDUFA goal date: February 18, 2014 & May 18, 2014, respectively

FDA issued a Background Package in preparation for this meeting on November 15, 2013.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 30 minutes (Microbiology Quality, Clinical)

Each issue will be introduced by FDA and followed by a discussion.

a. Microbiology Quality
   (i.) Endotoxin Testing Methodology

Discussion:
The Applicant indicated that it is planning to perform the additional testing, and asked about the acceptability of an alternative method. The FDA stated that it would require a complete review of the process to make this determination.

The Applicant also indicated that it would determine by January whether the low endotoxin recovery phenomenon is occurring; the FDA stated that this may be too late to be reviewed in the current review cycle, and may need to be addressed in a post-marketing commitment.

   (ii.) Rabbit Pyrogen Testing

Discussion:
The Applicant requested FDA input regarding preparation of the dosage for Rabbit Pyrogen Testing. The FDA indicated that dosing on a mg/kg basis similar to the doses studied in the clinical trials would be acceptable.

b. Clinical
   (i.) Efficacy: CD Induction

Discussion:
The Applicant requested clarification on the FDA position related to efficacy for maintenance in CD. The FDA stated that without evidence of efficacy for induction in CD, the Applicant may be unable to establish evidence of efficacy for maintenance in CD. Further discussion will occur at the AC.

   (ii.) Safety: Safety database, Indicated population, Concomitant immunosuppressive therapies

Discussion:
The Applicant asked for clarification on the number of postmarketing PML cases described in the FDA backgrounder in patients receiving natalizumab for CD. The FDA indicated that the cases listed in the FDA backgrounder were the only postmarketing cases known in patients receiving natalizumab for CD.

The applicant requested clarification from the FDA on what the "evidence threshold" is, as referred to in the DRISK section of the FDA backgrounder. The FDA clarified that there is no specific guidance or reference to what this specifically is, and that it will be a topic for discussion at the AC.

The Applicant asked for clarification related to the indicated population 'points for discussion' in the FDA backgrounder and if this is a vote or discussion question. The FDA commented that this determination has not yet been made, as the questions were still being developed.

3. Discussion of Minor Review Issues – 10 minutes (Microbiology Quality)

a) Quality
   - We do not agree with your response to our IR (dated Nov8, 2013) question C. The proposed acceptance criteria for potency assays in reference standard Requalification are too wide to provide adequate control over the drift in potency value of current reference standard. The potency results obtained for requalification of the current reference standards should be similar to the values obtained for current RS at the time of its initial qualification.

   - We disagree with the proposed specification acceptance criteria for potency assays (b) (4) as a specification method for evaluation of HCP.

Discussion:

The Applicant indicated that it has submitted information in response to the above. The FDA is still reviewing this information and was unable to comment.

b) Quality (Microbiology)

(i.) Container Closure Integrity Validation Testing:
The container closure integrity validation studies presented in BLA Module 3.2.P.2.4 did not include sufficient details regarding the [redacted] (b) (4), exposure, and dye concentration parameters used for performance of the dye and microbial ingress assays. The method sensitivity limit (minimum detectable perforation diameter) was also not indicated, [redacted] (b) (4) for rigorous validation of container system integrity. The studies should be repeated with positive controls containing perforations consistent with the method sensitivity limit.

Discussion:
The FDA indicated that the statement about the [redacted] (b) (4) hour post-constitution storage period in the proposed label is not acceptable without supporting microbiological quality validation studies. The label will be revised to state a 4 hour post-constitution storage period until there is data supporting a longer period than 4 hours.

The FDA also indicated that a third Quality Microbiology Drug Product information request would be issued shortly.

Discussions took place related to bulk hold period, and it was indicated from the Applicant that data will be ready after the review cycle. FDA indicated that this may become the subject of a post-marketing commitment.

2. Additional Applicant Data - 10 minutes (Applicant)

No additional discussion.

3. Ouststanding Information Requests – 10 minutes (RPM, Quality, Microbiology Quality)

(a) Quality

(i.) Per 21 CFR 610.14, "identity testing on the final drug product shall be performed after all labeling operations have been completed." Samples are currently pulled for release testing (including identity testing) prior to the time when the lot number is printed on the vial crimp (which we are allowing as substitution for having the actual label on the vial). To address this issue, Takeda needs to change their manufacturing process to ensure the DP identity testing is being performed on the correct (labeled) vials.

(b) (4)

(b) Microbiology Quality

(i.) November 13, 2013:

- Request for rabbit pyrogen test data.
- Request for data from spiking studies demonstrating that the polysorbate-containing drug product does not inhibit endotoxin detection by the LAL method.
- Request for data from container closure integrity validation studies performed with positive controls having perforations consistent with the method sensitivity limit.

(ii.) September 26, 2013:

- Request for microbiology data supporting a (b) (4) hour post-constitution hold period.

(iii.) November 14, 2013 (Drug Substance):

- Requests for updates to BLA related to microbial quality (b) (4) action limits and sample volumes and "Drug Substance (b) (4) performance test."

No additional discussion.

4. Discussion of Upcoming Advisory Committee Meeting – 10 minutes (FDA, Applicant)

Discussion:
The FDA asked the Applicant if it would be possible for them to consider an adjustment to the order of their presentations such that their PML expert presentation by Dr. Berger could occur first during their presentations. The Applicant will consider making this adjustment.

The Applicant noted that they had recently submitted an errata and requests for additional redactions to the Division of Advisory Committee and Consultant Management staff. The FDA stated that it is still reviewing this information.

The Applicant requested clarification on the analysis of C13006 and C13007 as it relates to the use of the Hochberg method vs. the Bonferroni method to control for multiplicity and if this could be clarified for the panel. The FDA stated that it will take the Applicant's request into consideration.

The Applicant noted that there were multiple points for consideration in the FDA backgrounder and requested the FDA to clarify which points would be the focus of questions for the committee. The FDA stated that the questions were still being developed, but there will likely be around seven questions focusing on the following: efficacy of UC, the efficacy of CD, safety, the benefit-risk assessment of UC, the benefit-risk assessment of CD, and safety and risk mitigation strategy considerations. The Applicant asked if they would all be voting or discussion questions. The FDA stated that the questions have not yet been finalized.

The Applicant again requested clarification on how the FDA planned to define "evidentiary threshold" and how it would fold into the questions for the committee. The FDA stated that this would be a topic for discussion at the AC.

The Applicant requested clarification on how the FDA was planning to ask any questions about the US vs. "Rest of World" populations. The FDA stated that a topic for discussion at the AC would be whether the labeling should reflect the population studied in the US or outside the US.

The Applicant questioned the FDA's plans for discussing risk management options with the committee, and if this will be presented as a binary decision. The Applicant raised its concern that the AC will only be given certain options that the FDA is proposing and not be given an opportunity to vote or discuss the Applicant's proposal for risk management.

5. REMS or Other Risk Management Actions – 5 minutes (DRISK, DPV, Applicant)

(a) Risk Management: Risk Management Strategies section of the FDA AC Briefing Document

(b) Pharmacovigilance: enhanced postmarketing surveillance for DILI/DIAIH and serious GI infections (such as C. difficile colitis, CMV colitis, Campylobacter gastroenteritis)

Discussion:
The FDA stated that any risk management issues will be discussed with the AC. The Applicant asked for the FDA's comment on the Applicant's proposed enhanced

pharmacovigilance plan. The FDA stated that it had not reviewed this, but will do so before the AC.

6. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

Please refer to our communication dated November 15, 2013, containing a current list of Postmarketing Commitments (PMCs); this list does not constitute a final list of post-approval requirements and/or commitments. Pending the outcomes of the December 9, 2013, Advisory Committee meeting, additional Postmarketing Requirements (PMRs) and/or Postmarketing Commitments (PMCs) may be communicated.

Discussion:
The FDA noted that since the LCM background package was sent to the Applicant, some of the CMC PMCs that were communicated on November 15, 2013, no longer apply based on the Applicant's responses to the FDA's requests for information.

7. Major labeling issues – 9 minutes (FDA Review Team)

Discussion:
The Applicant asked for clarification on why the FDA has revised the label related to the (b) (4) ***The FDA clarified that the data provided, and the design used, does not allow us to make this determination (time to treatment vs. dose effect).***

The Applicant stated that it is planning to submit additional analysis regarding the drug-drug interactions, which will address FDA's comments. The FDA encourages the applicant to conduct additional analysis based on direct comparisons of vedolizumab concentrations without relying on a model.

The FDA stated that in the absence of histologic data in the Phase 3 study, a claim of mucosal healing cannot be given to the product. The Applicant requested clarification around the mucosal healing endpoint revisions, and pointed out to the FDA that a Phase 2 study had been conducted in 2007 which included histologic data.

The Applicant inquired when it should respond to the labeling comments received on November 15, 2013. The FDA indicated that the Applicant should respond as soon as possible.

The mechanism of action in the clinical pharmacology section of the label was briefly discussed, with regards to the issue of gut selectivity vs. specificity. No agreement was made and the FDA stated that additional discussion could occur during labeling negotiations.

8. Review Plans – 1 minute (FDA Review Team)

We plan to convene an Advisory Committee meeting on December 9, 2013, and complete the reviews in accordance with the PDUFA goal dates.

No additional discussion.

9. Wrap-up and Action Items – 5 minutes (FDA Review Team / Applicant)

- ***AC TCON***
- ***Additional IR Responses from the Applicant***
- ***Labeling Negotiations to continue***

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/s/

ANIL K RAJPAL
12/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125476/0
BLA 125507/0

LATE CYCLE MEETING
BACKGROUND PACKAGE

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Colleen Costello, Ph.D.
Senior Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Dear Dr. Costello:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Entyvio (vedolizumab).

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 26, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Kevin Bugin, Senior Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Research and Evaluation

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 26, 2013, from 10:30 AM to 12:00 PM
Meeting Location: White Oak Building 02, Conference Room 2045
10903 New Hampshire Ave,
Silver Spring, MD 20903

Application Number: BLA 125476/0 & BLA 125507/0
Product Name: Entyvio (vedolizumab)
Indication: ulcerative colitis and Crohn's disease
Sponsor/Applicant Name: Takeda Pharmaceuticals U.S.A., Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review Letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Quality (Microbiology)

1. Endotoxin Testing Methodology:
   The vedolizumab drug product formulation contains excipients (e.g., polysorbate) that could result in low endotoxin recovery (LER). The applicant should provide results from studies conducted to assess if endotoxin recovery is affected by the polysorbate-containing vedolizumab drug product formulation. (b) (4) drug product test samples should be spiked with endotoxin and satisfactory endotoxin recoveries should be demonstrated over time. The spiking studies should be conducted in the same type of containers (b) (4) (b) (4)) in which the product and samples are held prior to endotoxin testing. In the event that spiked endotoxin cannot be recovered from formulated drug product, a path forward must be found for endotoxin release testing of the drug product.

2. Rabbit Pyrogen Testing:
   The Amendment 125476/0.25 (sequence 0025) response to Question 19 stated that the rabbit pyrogen test required by 21CFR 610.12(b) has not been performed. Due to the possibility of LER, equivalence using the LAL assay has not been verified. The LAL test is also not capable of detecting non-endotoxin pyrogens. The rabbit pyrogen test should be performed on three different drug product lots as per the requirements of USP <151>, Pyrogen Test, to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin.

Clinical

3. Efficacy:
   The key efficacy issue is whether substantial evidence of efficacy has been established for induction of clinical remission in CD. Of the two induction clinical trials in CD, only one met its primary endpoint.

4. Safety:
   The key safety issue is the risk of progressive multifocal leukoenceophalopathy (PML) which could potentially be caused by vedolizumab.

   a. Safety Database: There is uncertainty about the adequacy of the safety database to provide an acceptable pre-marketing assessment of this risk of PML.

   b. Indicated Population: Your proposed indicated population is patients that have failed either "conventional therapy" (which includes steroids and immunosuppressants) or TNFα-antagonists. We question if, given the potential

risk of PML, the appropriate indicated population should be patients that have been tried on steroids only or patients that have been tried on at least immunosuppressants.

c. Concomitant Immunosuppressive Therapies: Although a relationship between concomitant immunosuppressive therapies with infections was not found, there remains the concern that the risk of infections and of PML might be higher with concomitant immunosuppressive therapies. In the vedolizumab trials, these considerations led to the requirement that concomitant immunosuppressants will not be allowed beyond the induction phase (e.g., 6 weeks) in the US versions of the protocols. We question whether the labeling should have similar restrictions.

Refer to the Advisory Committee Meeting section, below, for additional information.

ADVISORY COMMITTEE MEETING

Date of AC meeting: December 9, 2013

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: November 15, 2013

Discussion topics that are potential questions for the Advisory Committee Meeting are as follows:

Efficacy - UC:

1. Evidence for vedolizumab efficacy for UC induction and for UC maintenance is provided by one trial each. Discuss if the available data support the efficacy of vedolizumab for the proposed UC induction and maintenance indications.

Efficacy - CD:

2. Evidence for vedolizumab efficacy for CD induction is provided by one trial but not replicated in a second trial in a refractory population. Evidence for vedolizumab efficacy for CD maintenance is provided in one trial. Discuss if the available data support the efficacy of vedolizumab for the proposed CD induction and maintenance indications.

3. Considering the currently available data, discuss whether additional efficacy studies should be obtained prior to approving vedolizumab for the proposed CD induction and maintenance indications.

Safety:

4. Consider whether the nonclinical data and human PD data presented for vedolizumab (e.g., specific α4β7 receptor binding target) provide sufficient evidence of less risk of PML than natalizumab.

5. Considering the currently available data, discuss whether additional safety data or studies should be obtained prior to approving vedolizumab for the proposed UC and/or CD indications.

Benefit-Risk Assessment for UC:

6. Based on currently available efficacy and safety data, discuss if the benefits outweigh the potential risks of vedolizumab (in particular, PML) for the proposed UC indications.

Benefit-Risk Assessment for CD:

7. Based on currently available efficacy and safety data, discuss if the benefits outweigh the potential risks of vedolizumab (in particular, PML) for the proposed CD indications.

Labeling and Risk Management Strategies:

8. Discuss if the indicated population should be limited to patients that have failed immunosuppressants or TNFα-antagonists or if the indicated population should include patients that failed steroids only.

9. Discuss if concomitant immunosuppressants should be limited to a specific duration (e.g., during induction only).

10. If you believe vedolizumab should be approved for the proposed UC or CD indications, discuss if risk management strategies beyond labeling are needed, and discuss the particular strategies.

Post-Approval Studies:

11. If you believe vedolizumab should be approved for the proposed UC or CD indications, discuss if any additional studies should be recommended post-approval.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming Advisory Committee meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location: http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

The REMS proposal review is ongoing. The results of the Advisory Committee meeting, including the discussion of the potential risk of PML and risk management approaches, may affect our final decision regarding the REMS.

We further refer to the Risk Management Strategies section of the FDA Advisory Committee Briefing Document for additional information on FDA's position related to the REMS for this product.

In addition, enhanced postmarketing surveillance for drug-induced liver injury (DILI)/drug-induced autoimmune hepatitis (DIAIH) and serious gastrointestinal (GI) infections (such as C. difficile colitis, CMV colitis, Campylobacter gastroenteritis) are being considered.

LCM AGENDA

1. **Introductory Comments – 5 minutes (RPM/CDTL)**

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. **Discussion of Substantive Review Issues – 30 minutes (Microbiology Quality, Clinical)**

   Each issue will be introduced by FDA and followed by a discussion.

   (a) Microbiology Quality
   (i.) Endotoxin Testing Methodology
   (ii.) Rabbit Pyrogen Testing

   (b) Clinical
   (i.) Efficacy: CD Induction
   (ii.) Safety: Safety database, Indicated population, Concomitant immunosuppressive therapies

3. **Discussion of Minor Review Issues – 10 minutes (Microbiology Quality)**

   a) Quality
      - We do not agree with your response to our IR (dated Nov8, 2013) question C. The proposed acceptance criteria for potency assays in reference standard Requalification are too wide to provide adequate control over the drift in potency value of current reference standard. The potency results obtained for requalification of the current

reference standards should be similar to the values obtained for current RS at the time of its initial qualification.

- We disagree with the proposed specification acceptance criteria for potency assays [redacted] (b) (4) as a specification method for evaluation of HCP.

b) Quality (Microbiology)

(i.) Container Closure Integrity Validation Testing:
The container closure integrity validation studies presented in BLA Module 3.2.P.2.4 did not include sufficient details regarding the [redacted] (b) (4) exposure, and dye concentration parameters used for performance of the dye and microbial ingress assays. The method sensitivity limit (minimum detectable perforation diameter) was also not indicated, [redacted] (b) (4) for rigorous validation of container system integrity. The studies should be repeated with positive controls containing perforations consistent with the method sensitivity limit.

3. Additional Applicant Data - 10 minutes (Applicant)

4. Ouststanding Information Requests – 10 minutes (RPM, Quality, Microbiology Quality)

(a) Quality

(i.) Per 21 CFR 610.14, "identity testing on the final drug product shall be performed after all labeling operations have been completed." Samples are currently pulled for release testing (including identity testing) prior to the time when the lot number is printed on the vial crimp (which we are allowing as substitution for having the actual label on the vial). To address this issue, Takeda needs to change their manufacturing process to ensure the DP identity testing is being performed on the correct (labeled) vials.

(ii.) [redacted] (b) (4)

(b) Microbiology Quality

(i.) November 13, 2013:

- Request for rabbit pyrogen test data.
- Request for data from spiking studies demonstrating that the polysorbate-containing drug product does not inhibit endotoxin detection by the LAL method.
- Request for data from container closure integrity validation studies performed with positive controls having perforations consistent with the method sensitivity limit.

(ii.) September 26, 2013:
- Request for microbiology data supporting a (b) (4) hour post-constitution hold period.

(iii.) November 14, 2013 (Drug Substance):
- Requests for updates to BLA related to microbial quality (b) (4) action limits and sample volumes and "Drug Substance (b) (4) performance test."

5. Discussion of Upcoming Advisory Committee Meeting – 10 minutes (FDA, Applicant)

6. REMS or Other Risk Management Actions – 5 minutes (DRISK, DPV, Applicant)

(a) Risk Management: Risk Management Strategies section of the FDA AC Briefing Document

(b) Pharmacovigilance: enhanced postmarketing surveillance for DILI/DIAIH and serious GI infections (such as C. difficile colitis, CMV colitis, Campylobacter gastroenteritis)

7. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

Please refer to our communication dated November 15, 2013, containing a current list of Postmarketing Commitments (PMCs); this list does not constitute a final list of post-approval requirements and/or commitments. Pending the outcomes of the December 9, 2013, Advisory Committee meeting, additional Postmarketing Requirements (PMRs) and/or Postmarketing Commitments (PMCs) may be communicated.

8. Major labeling issues – 9 minutes (FDA Review Team)

9. Review Plans – 1 minute (FDA Review Team)

We plan to convene an Advisory Committee meeting on December 9, 2013, and complete the reviews in accordance with the PDUFA goal dates.

10. Wrap-up and Action Items – 5 minutes (FDA Review Team / Applicant)

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/s/

ANDREW E MULBERG
11/15/2013
on behalf of Division Director, Dr Griebel