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RESEARCH**

APPLICATION NUMBER:

125476Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM TO OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	125476
Original Submission Dates	06/20/2013
PDUFA Due Date	05/18/2014
Brand Name	Entyvio
Generic Name	Vedolizumab
Primary Clinical Pharmacology Reviewer	Lanyan Fang, Ph.D.
Clinical Pharmacology Team Leader	Yow-Ming Wang, Ph.D.
Primary Pharmacometrics Reviewer	Justin Earp, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D. (Acting)
OCP Division	DCP III
OND Division	DGIEP
Sponsor	Takeda Pharmaceuticals
Relevant IND(s)	9125
Submission Type	NME
Formulation; Strength(s)	300 mg of lyophilized powder in a single-use vial
Proposed indication	Adult ulcerative colitis (UC) and Crohn's disease (CD)
Proposed Dosage and Administration	300 mg infused intravenously over approximately 30 minutes at Weeks zero, two and six, then every eight weeks (Q8W) thereafter.

This addendum documents the assessment of newly submitted drug-drug interaction information including new data/analyses received on 12/9/2013 (eCTD 0049).

BACKGROUND

The applicant proposed to label that co-administered immunomodulators (such as methotrexate, 6-mercaptopurine, and azathioprine) did not have a clinically meaningful effect on the pharmacokinetics (PK) of vedolizumab based on the results from population PK analysis submitted on 6/20/2013. The agency reviewed the population PK analysis and concluded that the analysis was not adequate to support this labeling claim due to the deficiency of the dataset (please refer to the clinical pharmacology review dated 11/8/2013 in DARRTS for more details). The primary concern was that the population PK modeling implemented the co-medication as a time-independent covariate. For instance, if a subject had a concomitant immunomodulator medication at any time in the treatment duration, this subject was labeled in the population model dataset as being on that co-medication all the time throughout the treatment duration. As such, all PK samples collected from that

individual were considered in the presence of co-medication, even if the subject did not take the co-medication at the time of sample collection for some samples. This deficiency was conveyed to the applicant during a face-to-face meeting on 11/26/2013. The applicant was also asked to provide a conventional analysis comparing the observed vedolizumab trough concentrations (C_{\min}) with or without co-medication in addition to the population PK model-based analysis.

Subsequently, the applicant submitted new data/analyses on 12/9/2013 to justify the proposed labeling claim, which is the subject of the current clinical pharmacology review addendum. Results of Sponsor's Analysis

1.1 Population PK Analysis

The applicant redefined their PK covariate (i.e., the status of co-medication) as a time-dependent variable. In the new population PK dataset, each PK timepoint was associated with a status of concomitant medication which was set to 1 for with co-medication or 0 for without co-medication based on the real-time administration record of co-medication. As a result of this revision to the dataset, the newly submitted analysis treated the co-medication as a time-dependent covariate, in particular to the linear CL (CL_L) in the PK model. The estimated covariate parameter value of 1 would indicate the co-medication does not impact CL_L and the extent of deviation from 1 would indicate the degree of effect of co-medication on CL_L . The sponsor reevaluated their NONMEM population PK model and provided the results based on this new analysis (Table 1). The population model estimates of linear CL (CL_L) and their corresponding 95% credible interval suggest that the presence of these concomitant medications do not impact vedolizumab PK.

Table 1. Covariate Parameter Estimates From the Sponsor's Updated Population Pharmacokinetic Model

Parameter	Estimates	Bayesian 95% Credible Interval
Categorical Covariates (Null effect =1)		
$CL_L \sim$ Azathioprine (θ_{16})	0.998	(0.964, 1.03)
$CL_L \sim$ Mercaptopurine (θ_{18})	1.04	(0.943, 1.15)
$CL_L \sim$ Methotrexate (θ_{20})	0.983	(0.899, 1.07)
$CL_L \sim$ Aminosaliclylates (θ_{22})	1.02	(0.988, 1.05)

Reviewer's Comments:

The sponsor's population PK model methodology appears reasonable and the results suggest that immunosuppressants did not impact the PK of vedolizumab.

1.2 Conventional Analysis of Observed C_{\min} Values

The applicant concluded that concomitant immunomodulators did not affect vedolizumab PK based on the observed vedolizumab trough concentrations (C_{\min}). The applicant calculated the summary statistics of vedolizumab trough concentrations at individual timepoints grouped by with or without concomitant immunomodulators. Summary statistics included mean (standard deviation), median and range (minimum and maximum). Vedolizumab PK profiles in ulcerative colitis (UC) and Crohns' disease (CD) were shown to be similar (refer to clinical pharmacology review dated 11/8/2013). As such, the applicant

pooled trough concentration data from Studies C13006 and C13007 for the analysis. Across multiple timepoints (Weeks 6, 14, 22, 38, 46, and 52) the summary statistics of vedolizumab C_{min} were generally similar for subjects with or without concomitant immunomodulators.

Reviewer's Comments:

Concomitant immunomodulators appear to have no impact on vedolizumab PK based on the observed vedolizumab trough concentrations. This is consistent with the results of the new population PK analysis.

2 REVIEWER'S ANALYSIS

2.1 Introduction

2.2 Objectives

The analysis objectives are:

1. To determine if the data quality is sufficient to conclude no interaction for methotrexate, 6-mercaptopurine, and azathioprine based on the population PK analysis.

2.3 Methods

2.3.1 Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Name	Link to EDR \\cdsesub1\bla\cCTD_Submissions\STN125476\
Tran02.csv	..\0049\m5\datasets\metrum-population-pk-pd\analysis\legacy\datasets\

2.3.2 Software

The following software packages were used in the analyses.

- S-plus (Tibco, Palo Alto, CA)
- NONMEM (Icon, Ellicott City, MD)

2.3.3 Models

No original models were developed as part of this review.

2.4 Results

2.4.1 Population PK Data Quality

Two aspects of data quality were reviewed for the sponsor's analysis: 1) the total number of subjects with concomitant medication and 2) that these data were at steady-state.

The numbers in Table 3 are the total number of subjects who were taking the respective concomitant medication for 100% of their time over which PK was collected. Based on an analysis by the AAPS working group for the assessment of therapeutic protein DDIs via population PK [1], 30 subjects with concomitant medication should be sufficient to conclude no effect when more than 100 individuals not receiving concomitant medication are in the dataset.

Also, to make sure that these individuals were at steady-state and not just on the drug for a couple of days, the median duration of the concomitant medication is also shown in Table 1.

Table 3. Numbers of Subjects and Duration on Concomitant Medications

Drug	N of Subjects taking conmed during 100% of PK Assessments	Median Duration of PK Assessments (Days) for those with 100% Conmeds
AZATHIOPRINE	486	250
BALSALAZIDE	29	323
MERCAPTOPYRINE	38	158
MESALAZINE	757	252
METHOTREXATE	52	93.4
OLSALAZINE	3	370
SULFASALAZINE	119	362

Based on these numbers and the results of the population PK analysis, it is reasonable to conclude that methotrexate, mercaptopurine, and azathioprine did not impact the pharmacokinetics of vedolizumab.

3 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
UpdatedDDITroughConc.ssc	PK DDI Data Quality Description	..\Reviews\PM Review Archive\2014\ \Vedolizumab_BLA125476_JCE\PPK Analyses\

4 REFERENCES

[1] Diane D Wang*, Min Zhu, Nastya Kassir, Hanley William, Justin Earp, Andrew Chow, Stefan Zajic, Manish Gupta, Chuanpu Hu. The Utility of a Population Approach in DDI Assessments: An Evaluation Using Simulation Approaches. Poster at the 2013 Annual American Conference on Pharmacometrics Meeting.

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/s/

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Primary Pharmacogenomics Reviewer	Sarah Dorff, Ph.D.
Pharmacogenomics Team Leader	Michael Pacanowski, Pharm.D.
OCP Division	DCP III
OND Division	DGIEP
Sponsor	Takeda Pharmaceuticals
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Proposed indication	Adult ulcerative colitis (UC) and Crohn's disease (CD)
Proposed Dosage and Administration	300 mg infused intravenously over approximately 30 minutes at Weeks zero, two and six, then every eight weeks (Q8W) thereafter.

This addendum provides the Individual Study Review for clinical pharmacology and clinical studies listed in Table 2 of the clinical pharmacology review of BLA 125476 (Vedolizumab).

Study C13001:

Study Title: A Phase 1, Single Ascending Dose, Randomized, Placebo-Controlled, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MLN0002 in Healthy Subjects

Study Objectives: The objectives of this study were to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of MLN0002 over a range of single IV doses, specifically:

- To assess the safety and tolerability of single intravenous (IV) doses of MLN0002
- To evaluate the single-dose PK of MLN0002
- To describe the extent and duration of MLN0002 binding to $\alpha_4\beta_7$ receptors on peripheral blood lymphocytes following IV administration of MLN0002
- To characterize the relationship between PK and PD of MLN0002

METHODS

Design: This was a randomized, placebo-controlled, double-blind, single ascending dose escalation study to investigate the safety, tolerability, PK, and PD of MLN0002 by cohort in healthy subjects. Each cohort consisted of 10 subjects (8 subjects randomized to receive MLN0002 and 2 subjects randomized to receive placebo). The dose of MLN0002 was increased sequentially from 0.2 to 10.0 mg/kg in 5 separate cohorts of subjects.

Diagnosis and Main Criteria for Inclusion: Medically healthy adults, aged 18 to 65 years, without clinically significant screening results and with a body mass index (BMI) between 18 and 32 kg/m², and body weight between 50 and 100 kg, inclusive, were eligible for enrollment in the study. Subjects were to be excluded from the study if they had previously received MLN0002.

Test Product, Dose and Mode of Administration: MLN0002, supplied as a frozen liquid; administered doses were 0.2, 0.5, 2.0, 6.0, and 10.0 mg/kg; IV infusion over 30 minutes.

Pharmacokinetic Assessments: PK blood samples were collected on Days 1 (prior to and 2 and 12 hours after the start of treatment administration), 2, 3, 4, 8, 15, 29, 43, 57, 71, and 85. Additional samples were collected from subjects in the 2.0 mg/kg cohort on Days 113 and 150 and from subjects in the 6.0 and 10.0 mg/kg cohorts on Days 113, 150, 164, 178, 192, and 206. MLN0002 concentrations in serum were measured and the PK parameters were determined from the serum concentration-time data using standard noncompartmental methods. The following MLN0002 PK parameters were estimated: C_{max} , $t_{1/2z}$, AUC_{0-last} , AUC_{0-inf} , CL, and V_z .

Pharmacodynamic Assessments: PD blood samples were collected on Days 1 (prior to and 2 and 12 hours after the start of treatment administration), 2, 3, 4, 8, 15, 29, 43, 57, 71, and 85. Additional samples were collected from subjects in the 2.0 mg/kg cohort on Days 113 and 150 and from subjects in the 6.0 and 10.0 mg/kg cohorts on Days 113, 150, 164, 178, 192, and 206. MAdCAM-1-Fc is a fusion of the $\alpha_4\beta_7$ ligand human mucosal addressin cell adhesion molecule-1 with the heavy and light chain Fc of a mouse monoclonal antibody.

The saturation and blockade of $\alpha_4\beta_7$ receptors were evaluated by noncompartmental methods and by plotting these variables over time.

RESULTS

Pharmacokinetic Results:

The PK parameters of MLN0002 following a 30-minute intravenous infusion of 0.2 to 10.0 mg/kg MLN0002 by cohort are summarized in Table 1.

Table 1 Overview of Vedolizumab PK by Dose Cohorts Following IV Infusion of 0.2 – 10 mg/kg in Healthy Subjects (Study C13001)

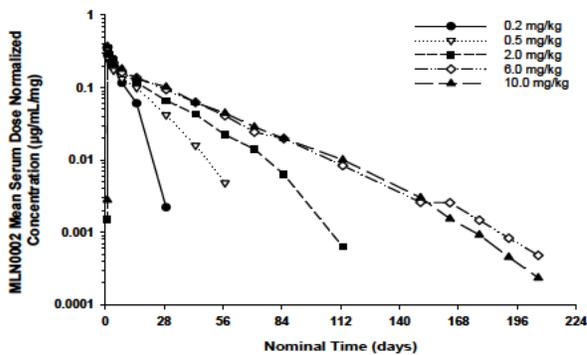
$t_{1/2}$ (day)

Maximum vedolizumab serum concentrations were achieved at or near the end of infusion and declined in a bi-exponential manner. Concentration-time profiles showed evidence of nonlinearity once concentrations reached approximately 1 to 10 $\mu\text{g/mL}$, suggesting clearance may increase at low concentrations as shown in Figure 1 and Figure 2.

Figure 1 Mean Concentration in Healthy Subjects Following Single-Dose Administration (log-linear plot) (C13001)



Figure 2 Dose-Normalized Mean Concentration by Nominal Actual Dose in Healthy Subjects Following Single-Dose Administration (log-linear plot) (C13001)



In subjects who developed HAHA to MLN0002, a faster clearance of MLN0002 was observed as compared to the HAHA-negative (HAHA-) subjects within the respective dose level.

Pharmacodynamic Results:

Vedolizumab inhibited Act-1 and MAdCAM-1-Fc binding to $\alpha_4\beta_7$ nearly maximally at all time points where vedolizumab was measurable in serum, indicating saturation of binding to $\alpha_4\beta_7$ by vedolizumab. Once vedolizumab concentrations decreased below the lower limit of detection of the assay, the extent of Act-1 and MAdCAM-1-Fc binding to $\alpha_4\beta_7$ returned to approximately the baseline levels. In some subjects who were HAHA positive, a faster loss of $\alpha_4\beta_7$ binding saturation by vedolizumab was observed as compared to HAHA negative subjects at the respective dose level (Table 2).

Table 2 Summary of Vedolizumab Pharmacodynamics (C13001)

(% Inhibition)
Source: Study
Abbreviation
to the last
Values are p
n = number of

CONCLUSIONS:

- MLN0002 demonstrated linear PK over the dose range 6-10 mg/kg and nonlinear PK over 0.2 to 2.0 mg/kg.
- The nonlinear PK suggested target-mediated drug disposition behavior of MLN0002. At dose levels greater than 2.0 mg/kg, no further changes in clearance values were observed, which suggests a saturable rapid elimination process for MLN0002 at low doses and a slower linear elimination process which is likely account for a large fraction of clearance of MLN0002 at higher doses.
- MLN0002 inhibited the binding of Act-1 and MAdCAM-1-Fc to $\alpha_4\beta_7$, at or near maximal levels at all time points when MLN0002 was measurable in serum. Once MLN0002 concentrations decreased below the limit of detection of the assay (0.125 $\mu\text{g/mL}$), the inhibition of Act-1 and MAdCAM-1-Fc returned to approximately the baseline level.
- In some subjects who developed HAHA to MLN0002, a faster clearance of MLN0002 and loss of $\alpha_4\beta_7$ receptor saturation was observed as compared to that of the HAHA- subjects within the respective dose level.

Study C13005:

Study Title: A Phase 1, Single Dose, Open-Label Study to Determine the Pharmacokinetics, Safety, and Tolerability of MLN0002 in Healthy Subjects Across a Range of Low and High Body Weights

Study Objectives: The objectives of this study were:

- To determine the pharmacokinetics (PK) of MLN0002 following a single 6.0 mg/kg intravenous (IV) dose of MLN0002 in healthy male and female subjects with low or high body weight
- To assess the safety and tolerability of MLN0002 following a single 6.0 mg/kg IV dose of MLN0002 in healthy subjects

METHODS

Design: This was an open-label, single-dose study designed to evaluate the PK, safety, and tolerability of MLN0002 in healthy subjects with high and low body weights. Male and female subjects between the ages of 18 and 65 years were enrolled in 2 cohorts: low body weight cohort and high body weight cohort. The low body weight cohort was defined as ≤ 60 kg for female subjects and ≤ 70 kg for male subjects; the high body weight cohort was defined as 90 to 130 kg (inclusive) for female subjects and 100 to 140 kg (inclusive) for male subjects. Subjects received a single dose of 6.0 mg/kg of MLN0002 via IV infusion over 30 minutes. PK samples and safety measurements were obtained for up to 206 days following study treatment.

Test Product, Dose and Mode of Administration, Lot Number: MLN0002, supplied as a frozen liquid; administered dose is 6.0 mg/kg; IV infusion over 30 minutes.

Pharmacokinetic Assessments: PK blood samples were collected on Days 1 (prior to and 2 and 12 hours after the start of treatment administration), 2, 4, 8, 15, 29, 43, 57, 71, 85, 113, 150, 164, 178, 192, and 206. MLN0002 concentrations in serum were measured, and the PK parameters were determined from the serum concentration-time data using standard noncompartmental methods. The following MLN0002 PK parameters were estimated: C_{\max} (observed maximum concentration); $t_{1/2}$ (terminal elimination half-life); $AUC_{0-t_{\text{las}}}$ (area under the drug concentration-time curve from administration time to the last measurement time point at which the concentration is above the lower limit of quantification); $AUC_{0-\infty}$ (area under the drug concentration-time curve, extrapolated to infinity); CL (total clearance); and V_z (volume of distribution based on the terminal phase).

RESULTS

Demographic Results: A total of 26 subjects (12 subjects in the low body weight group and 14 subjects in the high body weight group) were enrolled in the study and received the single dose of MLN0002. Twenty-three of the 26 subjects who received MLN0002 are included in the PK analysis set (10 subjects in the low body weight group and 13 subjects in the high body weight group). Overall, the proportion of female subjects was 58%. In the high body weight group there was an equal number of male and female subjects (7 [50%])

each), although there were twice as many female (8 [67%]) as male (4 [33%]) subjects in the low body weight group.

Pharmacokinetic Results: The PK parameters for MLN0002 following a 30-minute IV infusion of 6 mg/kg MLN0002 by cohort are summarized in the table below (Table 3).

Table 3 Summary of Vedolizumab PK parameters by Low and High Body Weight for MLN0002 at 6 mg/kg dose administered as a 30-min IV infusion

SD
Geometric Me
%CV
Median
Min
Max

As shown in the above table, mean vedolizumab exposures were higher in the subjects with high body weight (3220 day* $\mu\text{g}/\text{mL}$) compared to subjects with low body weight (2420 day* $\mu\text{g}/\text{mL}$), suggesting that weight-adjusted dosing overcompensated for exposure of vedolizumab in subjects with higher weight.

CONCLUSIONS: The PK data suggest that weight-adjusted dosing does not provide similar exposure of MLN0002 to subjects of varying body size. Therefore, fixed doses of vedolizumab were used in all subsequent studies including 4 phase 1 studies (C13009, C13010, C13012, and C13013), 4 phase 3 studies (C13006, C13007, C13008, and C13011). MLN0002 was well tolerated when administered IV as a single dose of 6 mg/kg to healthy subjects of low or high body weight.

Study C13009:

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

Study Objectives: The objectives of this study were:

- To determine the pharmacokinetics (PK) and pharmacodynamics (PD) of a single intravenous (IV) 300 mg dose of the Process C drug product of MLN0002
- To determine the PK and PD of a single IV 600 mg dose of the Process C drug product of MLN0002 relative to the Process B drug product of MLN0002
- To assess the safety and tolerability of a single IV dose of the Process C drug product of MLN0002
- To evaluate the effect of MLN0002 on cardiac repolarization [Note: see interdisciplinary QT review for results]

METHODS

Study Design: The study comprises 2 parts:

- Part 1, an open-label study of a single dose of IV 300 mg MLN0002; where subjects received Process C drug product, and
- Part 2, a randomized, placebo-controlled, double-blind, parallel-group study of a single dose of IV 600 mg MLN0002; where subjects were randomized in a 1:1:1 ratio to receive IV 600 mg Process B drug product, 600 mg Process C drug product, or placebo.

Diagnosis and Main Criteria for Inclusion: Healthy male and female subjects between the ages of 18 and 45 years with body mass index (BMI) between 18 and 32 kg/m², inclusive.

Test Product, Dose and Mode of Administration, Batch Number:

- Process B drug product (MLN0002 (b) (4)), supplied as a frozen liquid dosage form in 10 mL vials; 600 mg; Batch number: IB004SA01.
- Process C drug product (MLN0002 (b) (4)), lyophilized solid formulation; 300 mg or 600 mg; Batch number: IC006LA01.

Each product was administered by intravenous infusion in 250 mL solution of 0.9% sodium chloride over a 30-minute period.

Pharmacokinetic Assessments: PK blood samples were collected on Day 1 (prior to the start of study drug infusion, 5 minutes after the end of infusion, and 1, 2, and 12 hours after the start of infusion), and Days 2 (± 2 days), 8 (± 2 days), 29 (± 2 days), 57 (± 2 days), 85 (± 2 days), 113 (± 2 days), 141 (± 2 days), 169 (± 2 days), and 197 (± 2 days). Only PK samples from subjects randomized to active treatment were planned for analysis. The following MLN0002 PK parameters were estimated: C_{max} (maximum drug concentration); $t_{1/2}$ (terminal half-life [if possible]); AUC_{0-last} (area under the drug concentration-time curve from administration time to the last measurement time point at which the concentration is above the lower limit of quantification); AUC_{0-inf} (area under the drug concentration-time curve, extrapolated to infinity [if possible]); CL (total clearance following the dose

administered [if possible]); V_{ss} (steady state volume of distribution); V_z (volume of distribution based on the terminal phase [if possible]); and MRT (mean residence time [if possible]).

Pharmacodynamic Assessments: PD blood samples were collected on Days 1 (prior to the start study drug infusion), 2, 8, 29, 57, 85, 113, 141, 169, and 197. Only PD samples from subjects randomized to active treatment were planned for analysis. PD blood samples were analyzed for the presence of MLN0002 on the surface of cells bearing the $\alpha_4\beta_7$ integrin. Analysis of these samples consisted of 2 validated flow cytometric assays: (1) ACT-1 Binding Interference Assay and (2) MAdCAM-1-Fc Binding Interference Assay.

Immunophenotyping Assessments: Based on the similarity in mechanism of action between natalizumab and MLN0002, peripheral blood samples were examined for the effect of MLN0002 on CD34+ HPCs and target cell populations (CD4+CD45RO+CD25+ and CD8+CD45RO+CD25+ cells expressing high levels of integrin β_7). Immunophenotyping samples were collected on Days 1 (prior to the start study drug infusion), 2, 8, 29, 113, 141, and 197 from 15 subjects receiving MLN0002 (comprised of 12 subjects from Part 1 receiving 300 mg Process C MLN0002 and 3 subjects from Part 2, 2 of which received 600 mg of Process B MLN0002 and 1 who received 600 mg of Process C MLN0002) and 19 subjects receiving placebo (Part 2). Quantitation was performed using flow cytometry.

RESULTS

Subject Disposition: A total of 87 subjects were enrolled in the study (13 subjects in Part 1, and 74 subjects in Part 2). In Part 2, 23 subjects were randomized to a single IV dose of 600-mg Process B MLN0002, 26 subjects were randomized to a single IV dose of 600-mg Process C MLN0002, and 25 subjects were randomized to a single IV dose of placebo.

All 87 subjects were included in the safety population, and 56 subjects (10, 22, and 24 subjects in the 300-mg Process C MLN0002, 600-mg Process B MLN0002, and 600-mg Process C treatment groups MLN0002, respectively) were included in the PK and PD analysis populations.

Seventy-three subjects were included in the primary ECG population and 71 subjects were included in the secondary ECG population. A total of 66 (76%) subjects completed the study; 8 (9%) subjects withdrew their consent and 13 (15%) subjects were lost to follow-up.

Pharmacokinetic Results:

PK profiles:

Following the 30-minute, IV infusion administration of MLN0002 on Day 1, after reaching peak concentration, serum concentration of MLN0002 fell in a biphasic manner beginning with a rapid distribution phase followed by a slower elimination phase. The mean concentration time profiles for 600-mg Process B and Process C MLN0002 are superimposable as shown below (Figure 3, Figure 4).

Figure 3 Linear Plot of Mean MLN0002 Serum Concentrations Over Time by Treatment Group (Pharmacokinetic Analysis Set)

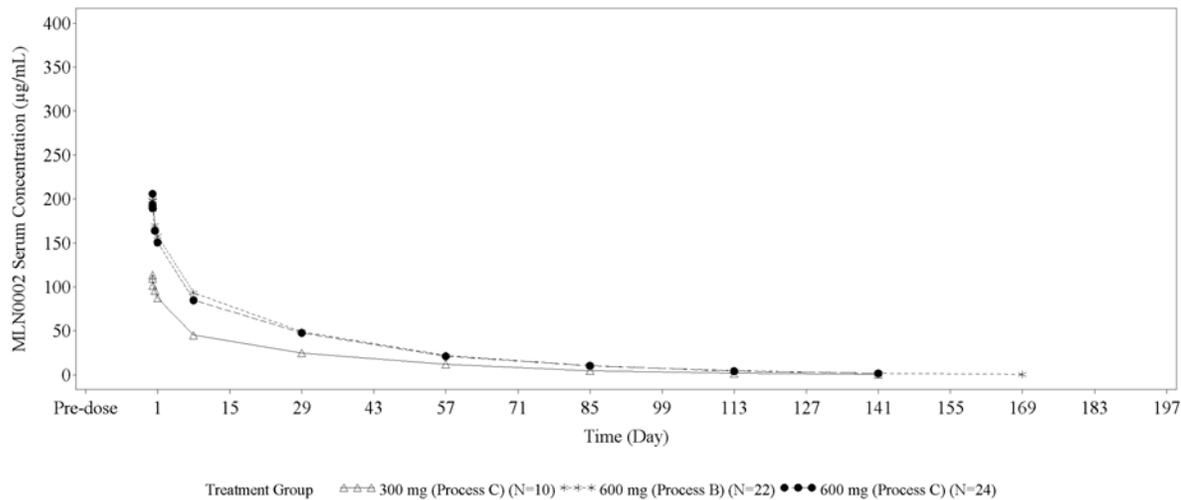
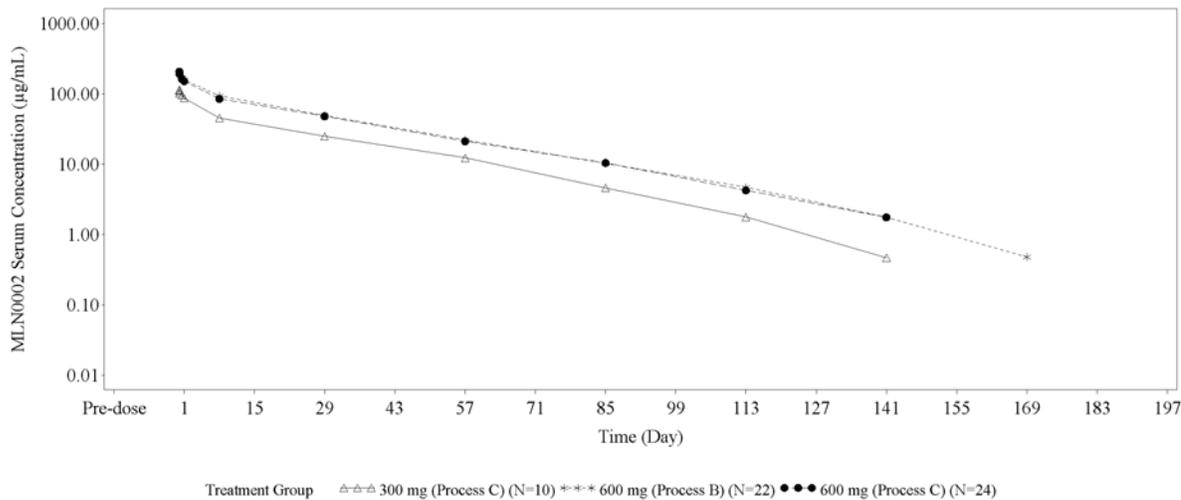


Figure 4 Semilogarithmic Plot of Mean MLN0002 Serum Concentrations Over Time by Treatment Group (Pharmacokinetic Analysis Set)



As expected for IV infusion administration, C_{max} was achieved in most subjects at 5 minutes following the end of infusion. A summary of the PK parameters is shown in Table 4. C_{max} was dose proportional across the doses tested in the study. Subjects receiving 300-mg Process C had a geometric mean C_{max} of 115 µg/mL. Subjects receiving 600-mg Process C MLN0002 (2-fold dose increase) had an approximately 2-fold higher C_{max} (206 µg/mL) relative to the 300-mg treatment group. C_{max} was similar in subjects receiving 600-mg Process B and Process C MLN0002 (205 µg/mL and 206 µg/mL, respectively). AUC_{0-inf} was dose proportional across the doses tested in the study. Subjects receiving 300-mg Process C MLN0002 had a geometric mean AUC_{0-inf} of 2000 d*µg/mL. Subjects receiving 600-mg Process C MLN0002 had an approximately 2-fold higher geometric mean AUC_{0-inf} (3890 d*µg/mL) relative to the 300-mg Process C MLN0002 treatment group. AUC_{0-inf} was similar

between subjects receiving 600-mg Process B and Process C MLN0002 (4040 µg/mL and 3890 µg/mL, respectively). The mean CL was similar across the treatment groups (151, 157, and 149 mL/day for the 300-mg Process C MLN0002, 600-mg Process C and Process B MLN0002 treatment groups, respectively). The mean $t_{1/2}$ was similar across the treatment groups (18.3, 21.0, and 19.4 days for the 300-mg Process C MLN0002, 600-mg Process C and Process B MLN0002 treatment groups, respectively). The mean V_{ss} was similar across the treatment groups (4.53, 5.04, and 4.73 L for the 300-mg Process C MLN0002, 600-mg Process C and Process B MLN0002 treatment groups, respectively). Similarly, the mean V_z was 3.93, 4.74, and 4.12 L for the 300-mg Process C MLN0002, 600-mg Process C and Process B MLN0002 treatment groups, respectively. These estimates are consistent with the predicted distribution volume of large protein therapeutics.

Comparability of Process B and Process C Product

calculated treatment mean ratios and associated 90% CIs for both the C_{max} and AUC_{0-inf} parameters for the 600-mg Process B compared to 600-mg Process C treatment groups. The results demonstrated that the 2 process groups were very similar (Table 5).

Table 4. Summary of Vedolizumab PK parameters in Study C13009 [geometric mean(%CV)]

Parameter	Process B	Process C
C_{max}	151	157
AUC_{0-inf}	151	157
$t_{1/2}$ (days)	18.3	19.4
CL (L/day)	151	149
V_z (L)	3.93	4.12
V_{ss} (L)	4.53	4.73

n = 10 for C_{max} and n=10 for all other parameters
n = 22 for C_{max} and n=22 for all other parameters
n = 19 for C_{max} and n=19 for all other parameters

Table 5. Statistical Summary of Vedolizumab PK Comparability Data in Study C13009 (geometric mean ratio and 90% CI)

Parameter	Process B	Process C
C_{max}	151	157
AUC_{0-inf}	151	157

n = 21 for C_{max} and n=19 for AUC_{0-inf}
n = 24 for C_{max} and n=22 for AUC_{0-inf}

The data suggest that the PK of the products from 2 processes meet the criteria for bioequivalence (i.e., the 90% CIs for the geometric mean ratios of AUC_{inf} and C_{max} fell within the range of 80% to 125%). Therefore, Process B and Process C drug products were considered comparable based on PK comparability.

Source	Abbreviation
	C_m

HAHA Results:

Overall, 5 (8%) subjects were positive for HAHA, all of whom were receiving active treatment. HAHA+ was persistent in 4 of 5 subjects and transient in one subject. Of the time points where a measurement was made, HAHA were most frequently observed on Day 29 and Day 197 (2 subjects each). A total of 4 (6%) subjects had neutralizing HAHA.

Pharmacodynamic Results: Following the 30-minute IV infusion administration of MLN0002, near maximal inhibition of ACT-1 and MAdCAM-1-Fc binding was achieved by the time of the first PD sampling (24 hours after the end of the infusion) in all treatment groups. Based on graphical evaluation of MAdCAM-1-Fc binding time-course, the loss of near maximal inhibition (i.e., > 10% of baseline) occurred at Day 144 in the 300-mg treatment group and occurred by Day 169 in both 600-mg treatment groups. The maximum effect (E_{max}) of MLN0002 was approximately 99% for all treatment groups as measured by the ACT-1 markers and approximately 98% based on MAdCAM-1-Fc for all treatment groups. No dose- or concentration-response relationship in regard to E_{max} was detectable as all concentrations of MLN0002 following the 300- and the 600-mg dose maximally inhibited the binding of both ACT-1 and MAdCAM-1Fc.

Immunophenotyping Results: There was no difference in CD34+ HPC levels between subjects receiving a single dose of MLN0002 versus placebo through day 197. An increase in CD3+CD4+CD45RO+CD25+ β 7+ and CD3+CD8+CD45RO+CD25+ β 7+ cells, cell types that are relevant to the mechanism of action of MLN0002, was observed. The maximal increase (Day 8) occurred in < 2% of CD3+ cells and did not increase total circulating lymphocytes or leukocytes. An increase in CD3+CD4+CD45RO+CD25+ β 7+ and CD3+CD8+CD45RO+CD25+ β 7+ cells was also observed between Days 141 and 197, during which time drug concentration was below detectable limits.

QT results:

Please refer to section 2.2.6.4 of QBR review and interdisciplinary QT review for more details.

Study C13012

Study Title: A Phase 1 Single-Arm Study to Evaluate the Effects of a Single Intravenous Dose of Vedolizumab (MLN0002) on the CD4⁺:CD8⁺ Lymphocyte Ratio in the Cerebrospinal Fluid of Healthy Subjects

Study Objectives:

- To evaluate the change in cerebrospinal fluid (CSF) CD4⁺:CD8⁺ lymphocyte ratio before and after a single 450-mg intravenous (IV) dose of vedolizumab
- To determine if reversal of the normal CSF CD4⁺:CD8⁺ lymphocyte ratio to < 1 occurs after a single 450-mg IV dose of vedolizumab
- To assess the safety and tolerability of a single 450-mg IV dose of vedolizumab

METHODS

Design: This was a phase 1, single-arm, open-label study designed to investigate the effect of a single 450-mg IV dose of vedolizumab on the CD4⁺:CD8⁺ T-lymphocyte ratio in CSF in healthy subjects. Fourteen subjects were enrolled in the study. A subject was considered to be enrolled when he/she had received any amount of study drug. Cerebrospinal fluid was obtained by lumbar puncture (LP) prior to and 5 weeks after administration of a single 450-mg IV dose of vedolizumab. The study design included a screening period (Days -28 to -1), a treatment period (Day 1), and an observation/sampling period (Day 1 through Week 16).

Diagnosis and Main Criteria for Inclusion: Healthy male and female subjects between the ages of 18 and 45 years with body mass index (BMI) between 18 and 32 kg/m², inclusive, who had no significant medical problems and did not use concomitant immunosuppressive medications, were eligible for enrollment.

Test Product, Dose and Mode of Administration: Vedolizumab lyophilized powder for reconstitution, 60 mg/mL reconstituted solution; administered dose was 450 mg; IV infusion.

Duration of Treatment: Single dose, with observation for up to 16 weeks post dose

Pharmacokinetic Assessments: Blood samples were collected for the determination of serum vedolizumab concentrations on Day 1 (predose and postdose), and at Weeks 5 and 16. Vedolizumab concentration in CSF was determined from CSF samples obtained at baseline and at Week 5.

Pharmacodynamic Assessments: Blood samples were collected for the determination of MAdCAM-1-Fc binding, indicative of the extent of $\alpha_4\beta_7$ receptor saturation by vedolizumab in order to determine if adequate target saturation was achieved at the time of endpoint analyses (Week 5). Blood samples were collected on Day 1 (predose) and at Week 5.

Immunophenotyping Assessments: Cerebrospinal fluid was collected during screening and at Week 5 for measurement of T lymphocytes expressing CD4⁺ and CD8⁺ and the ratio of CD4⁺ to CD8⁺ lymphocytes. In parallel with CSF assessments, a peripheral blood sample

was obtained during screening and at Weeks 2, 5, and 16 to evaluate the effect of vedolizumab on peripheral cell populations.

Other Assessments: Immunogenicity (HAHA and Neutralizing HAHA) Assessments

Blood samples for the assessment of HAHA were collected at Day 1, Week 5 and Week 16. On days when both HAHA and pharmacokinetic (PK) sampling were required, the sample collections were timed as close to each other as feasible. The sample collected for HAHA analysis could also be assessed for neutralizing HAHA if HAHA was detected.

RESULTS

Disposition: All 14 enrolled subjects received vedolizumab and were included in the Safety Population. The applicant excluded one subject (Subject 030) from the CD4⁺:CD8⁺ Evaluable Population, Pharmacodynamics Population, and Serum PK Population because this subject was HAHA+ at Weeks 5 and 16. However, the applicant included this subject in the CSF PK Population. As this subject had significantly lower serum vedolizumab concentration at Week 5, it is biased to include this subject in the CSF PK Population but not in the Serum PK Population. Twelve subjects (86%) were included in the CD4⁺:CD8⁺ Evaluable Population with Week 16 Assessments (completed the study) for the additional sensitivity analyses.

Pharmacokinetic Results: At 5 minutes after the end of the 30-minute IV infusion of vedolizumab 450 mg, the median peak serum vedolizumab concentration value was 187 µg/mL, which declined to a median serum vedolizumab concentration of 32.5 µg/mL at Week 5, the time point of the endpoint assessment. None of the CSF samples obtained prior to and at 5 weeks after the infusion of vedolizumab had detectable vedolizumab (detection limit of vedolizumab in this assay was 0.125 µg/mL). These data indicate that no measurable vedolizumab was distributed into the CSF despite at 5 weeks after the single 450 mg IV administration. Please refer to section 2.2.7.5 of QBR review for clinical relevance of this data.

In the single subject (Subject 030) who developed detectable HAHA at Week 5 and was excluded from the Serum Pharmacokinetics Population, the serum concentration of vedolizumab at Week 5 was approximately 0.4 µg/mL, which was approximately 1.23% of the median Week 5 vedolizumab concentration (32.5 µg/mL) among subjects who did not have detectable HAHA. This subject did not have measurable serum concentrations of vedolizumab at Week 16.

Pharmacodynamic Results: The PD marker, MAdCAM-1-Fc, was used to evaluate the extent of α4β7 receptor binding saturation by vedolizumab; a decrease in MAdCAM-1-Fc binding relative to baseline values is a marker of α4β7 receptor binding by vedolizumab. The relationship between the serum concentration of vedolizumab at Week 5 and the percent decrease from baseline in MAdCAM-1-Fc binding for CD4⁺ and CD8⁺ cell population was assessed. Over the serum concentration range of vedolizumab observed, there was a high degree of saturation (> 90%) of the α4β7 receptor at Week 5 in most subjects as shown by the low percentage of free binding sites available to bind to MAdCAM-Fc.

Immunophenotyping Results:

Cerebrospinal Fluid Immunophenotyping: One of 14 subject was excluded from the CSF CD4⁺:CD8⁺ Evaluable Population because HAHA was detectable at Weeks 5 and 16; thus, the population for analyses of CSF endpoints had N = 13. Results showed that vedolizumab did not alter the CSF CD4⁺:CD8⁺ lymphocyte ratio in healthy subjects after a 450-mg single dose (Figure 5).

Figure 5 Cerebrospinal Fluid CD4+:CD8+ Ratio Before and After Vedolizumab Administration to Healthy Subjects (C13012)

Abbreviation: CI = confidence interval.

Baseline is defined as the value collected at the time closest to, but prior to, the start of study drug administration. The figure shows ratios for each subject before and after vedolizumab dosing, connected by dotted lines. The solid lines represent the group mean CD4⁺-to-CD8⁺ ratios at baseline and Week 5.

There were no significant changes in mean and median absolute cell counts and essentially no change in the mean percentages of CD4⁺ and CD8⁺ expressing T lymphocytes in the CSF from baseline to Week 5. The mean change in percent CD4⁺ and CD8⁺ cells in the CSF after a single dose of vedolizumab was < 1% (Figure 6).

Figure 6 Cerebrospinal Fluid CD4⁺ and CD8⁺ Lymphocytes Counts by Study Visit (C13012)

A) CD4⁺ Lymphocytes

B) CD8⁺ Lymphocytes

Baseline is defined as the value collected at the time closest to, but before, the start of study drug administration. The center horizontal line in each box corresponds to the median. The upper and lower box margins correspond to the 75th and 25th percentiles. The bars on each outer end correspond to the most extreme point less than or equal to 1.5 times the interquartile range. The points outside these lines represent outliers.

As stated in the QBR review, the clinical relevance of these findings in healthy subjects is unclear.

Immunogenicity: One of the 14 subjects in the Safety Population had detectable HAHA (Subject 030). This subject had a HAHA titer of 1:125 at Weeks 5 and 16, and rapidly cleared vedolizumab from the serum (as noted previously, the Week 5 serum concentration for this subject was 0.4 µg/mL, approximately 1.23% of the median concentration of 32.5 µg/mL observed for subjects who did not test positive for HAHA). No further neutralization testing was performed.

Study C13002

Study Title: A Phase 2, Randomized, Placebo-Controlled, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MLN0002 Following Multiple Intravenous Doses in Patients with Ulcerative Colitis

Study Objectives:

- To assess the safety and tolerability of a range of multiple intravenous (IV) doses of MLN0002 in subjects with ulcerative colitis (UC)
- To define the multiple-dose pharmacokinetics (PK) of MLN0002 for a range of IV doses in subjects with UC
- To describe the extent and duration of MLN0002 binding to $\alpha_4\beta_7$ receptors on peripheral blood lymphocytes following a range of multiple IV doses of MLN0002
- To characterize the relationship between the PK and pharmacodynamics (PD) of MLN0002 over a range of multiple IV doses of MLN0002 in subjects with UC

METHODS

Design: This was a randomized, placebo-controlled, double-blind trial to evaluate the safety, tolerability, PK, and PD of multiple IV doses of 2.0, 6.0, or 10.0 mg/kg MLN0002 or placebo administered on Days 1, 15, 29, and 85 in subjects with active UC. Subjects entered into 1 of 2 different PK/PD sampling schedules: the standard or the reduced PK/PD sampling schedule.

This study was initiated with a dose of 6.0 mg/kg. The first 5 subjects enrolled were randomized 4:1 to 6.0 mg/kg MLN0002 or placebo. A safety review of all available data was conducted within 1 week after the fifth subject was dosed to ensure that no safety events had occurred that would affect subsequent enrollment across all 3 cohorts. Randomization into all 3 cohorts (2.0, 6.0, and 10.0 mg/kg) then ensued.

Diagnosis and Main Criteria for Inclusion: Male or female patients with active UC, aged 18 to 70 years. Subjects had UC symptoms for a minimum duration of 2 months in conjunction with endoscopic and/or histopathological documentation consistent with UC and had known disease involvement extending proximal to the rectum. Subjects were ambulatory and experiencing disease activity documented with a partial Mayo score of 1 to 7. Subjects were excluded from the study if they had previously received MLN0002, had other major gastrointestinal conditions or infections, or had a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist at screening.

Test Product, Dose and Mode of Administration: MLN0002, supplied as a frozen liquid; administered doses were 2.0, 6.0, or 10.0 mg/kg; IV infusion over 30 minutes.

Pharmacokinetic Assessments: Blood samples for PK evaluation were collected at multiple time points following study drug administration. MLN0002 concentrations in serum were measured by enzyme-linked immunosorbent assay (ELISA) and the PK parameters were determined from the serum concentration-time data using standard noncompartmental methods.

Pharmacodynamic Assessments: Blood samples for PD evaluation were collected at multiple time points following study drug administration and were analyzed to demonstrate the presence of MLN0002 on the surface of cells bearing the $\alpha_4\beta_7$ integrin. Analysis of PD samples consisted of 2 flow cytometric assays, (1) Act-1 binding interference assay, and (2) MAdCAM-1-Fc binding interference assay. The PD parameters (the extent and duration of binding to the $\alpha_4\beta_7$ receptor) of MLN0002 to be analyzed for the PD markers, Act-1 and MAdCAM-1-Fc, were determined from serum PD-time data using standard noncompartmental methods.

Pharmacogenetic Assessments: The relationship between response to MLN0002 (measured by the change in partial Mayo score) and the following individual SNPs was to be examined: IL23R, NOD1, NOD2, SLC22A4, MAdCAM-1, CARD8, and β_7 . The SNPs were to be sequenced from DNA isolated from blood samples of enrolled subjects drawn at screening.

Exploratory Efficacy Assessments: The partial Mayo score was used to monitor changes in UC disease activity during treatment with MLN0002. A partial Mayo score was obtained during screening and on Days 1, 15, 29, 43, 85, 113, 169, 197, and 253.

RESULTS

Disposition: A total of 56 subjects were screened of whom 47 subjects were randomized and 46 subjects were dosed with study drug treatment; all 46 subjects were included in the safety assessment. One subject in the 2.0 mg/kg cohort (Subject 212-001) was found to have a positive purified protein derivative (PPD) for tuberculosis after randomization and was never dosed. A total of 37 subjects received at least 1 dose of MLN0002 (12 subjects received 2.0 mg/kg MLN0002, 14 subjects received 6.0 mg/kg MLN0002, and 11 subjects received 10.0 mg/kg MLN0002) and 9 subjects received at least 1 dose of placebo. A total of 35 subjects were included in the PK analysis set (10 in 2.0 mg/kg, 14 in 6.0 mg/kg, and 11 in 10.0 mg/kg cohorts). A total of 33 subjects were included in the PD analysis set (10 in 2.0 mg/kg, 12 in 6.0 mg/kg, and 11 in 10.0 mg/kg cohorts). Two subjects did not complete the study: 1 subject (placebo) withdrew early at Day 197, with sponsor approval, in order to enter the C13004 open-label study; the other subject (2.0 mg/kg MLN0002) withdrew consent, missed the Day 85 dose, and was considered to be terminated from the study 91 days after the last dose of study treatment.

Pharmacokinetic Results: The PK parameters for MLN0002 following a 30-minute IV infusion of 2.0 to 10.0 mg/kg MLN0002 by dose cohort are summarized in the table below (Table 6).

Table 6 Summary of Vedolizumab PK parameters by Dose Cohort After 4 doses of Vedolizumab Administered on Days 1, 15, 29, and 85.

$\frac{AUC_{(Day\ 85)}}{(day \cdot \mu g/m)}$

$t_{1/2}$ (day)

Pre-dose MLN0002 concentrations collected on Days 15 and 29 generally increased relative to the pre-dose concentration Day 1 which is consistent with the relative long half-life (~ 20 days).

In general, the C_{max} increased with increasing dose in a linear manner on both Day 1 and Day 85. The C_{max} on Day 85 was approximately 1.0-fold to 1.2-fold higher than the Day 1 C_{max} across all dose cohorts. The 14-day AUC increased with increasing dose in a linear manner following first dose and the fourth dose. Comparing between Day 1 and Day 85, the AUC for the 14-day post dose interval after last dose at Day 85 was approximately 1.3-fold to 1.5-fold higher across all dose cohorts compared to that after the first dose.

Pharmacodynamic Results: The PD parameters of MLN0002 following a 30-minute IV infusion of 2.0 to 10.0 mg/kg MLN0002 by dose cohort are summarized in the tables below for MAdCAM-1-Fc (Table 7).

Table 7 Summary of Emax and AUEC (area under the drug effect-time curve) as Measured by Percent Inhibition of %MAdCAM⁺ by Dose Cohort (PD Analysis Set)

E_{max, All}
(% Inhibition)

AUEC_(0-last)
(% Inhibition)

MLN0002 inhibited the binding of the PD marker, MAdCAM-1-Fc, nearly completely across all dose cohorts and the time of the maximal effect generally occurred at the first sample time for each subject. Additionally, once MLN0002 concentrations decreased to levels at or below the limit of detection of the assay, the percent inhibition of Act-1 and MAdCAM-1-Fc returned to approximately the baseline level.

In 1 of 2 subjects who were persistently positive for HAHA, a faster clearance of MLN0002 and loss of $\alpha_4\beta_7$ receptor saturation was observed as compared to the HAHA- subjects within the respective dose level.

Pharmacogenetic (PG) Results:

Please refer to Appendix of QBR review for PG results.

CONCLUSIONS

In conclusion, MLN0002 demonstrated linear PK over the dose range 2.0 to 10.0 mg/kg in UC patients. MLN0002 inhibited the PD marker, MAdCAM-1-Fc, nearly completely across all dose cohorts.

Study C13006

Study Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis

Study Objectives:

Induction Phase

- To determine the effect of vedolizumab induction treatment on clinical response at 6 weeks
- To determine the effect of vedolizumab induction treatment on clinical remission at 6 weeks
- To determine the effect of vedolizumab induction treatment on mucosal healing at 6 weeks

Maintenance Phase

- To determine the effect of vedolizumab maintenance treatment on clinical remission at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on durability of clinical response
- To determine the effect of vedolizumab maintenance treatment on mucosal healing at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on durability of clinical remission
- To determine the effect of vedolizumab maintenance treatment on corticosteroid-free remission at 52 weeks

METHODS

Design: This phase 3, randomized, blinded, placebo-controlled study in patients with moderately to severely active UC comprises 2 phases (refer to Figure 7).

Specifically, “Induction Study” refers to the placebo-controlled format, planned induction efficacy analyses of the effects of vedolizumab administered at Weeks 0 and 2;

“Maintenance Study” refers to the placebo-controlled format, planned maintenance efficacy analyses of vedolizumab administered as maintenance therapy in patients who had achieved clinical response during induction.

The Induction Phase began at Week 0, included study drug dosing at Weeks 0 and 2, and concluded with induction-related assessments at Week 6. Patients who completed the Induction Phase entered into the Maintenance Phase, which began at Week 6, included study drug dosing at Week 6 and every 4 weeks (Q4W) thereafter, and concluded with Week 52 assessments.

Figure 7 Treatment Phases, Study Drug Randomization, and Treatment Assignment Scheme

Induction Phase: There were 2 sequential Induction Phase cohorts of enrolled patients. Eligible patients enrolled in Cohort 1 were randomized in a 3:2 ratio to double-blind vedolizumab 300 mg or placebo administered intravenously. The number of patients enrolled into Cohort 1 was determined by the sample size requirements for the Induction Study efficacy analyses. After Cohort 1 enrollment was completed, additional patients were enrolled into Cohort 2, in order to provide sufficient numbers of patients to fully power the Maintenance Study efficacy analyses. All patients in Cohort 2 received open-label vedolizumab, administered at a dose of 300 mg at Weeks 0 and 2. Efficacy was assessed at Week 6 for all patients. The Induction Study efficacy analyses were based on the assessments performed on patients included in the randomized, double-blind treatment groups in Cohort 1 (Intend to treat, ITT Population). Safety analyses for the Induction Phase include all safety data collected from baseline (Week 0) through the Week 6 induction assessments, summarized by Induction Phase treatment group.

Maintenance Phase: The Maintenance Phase began after the Week 6 efficacy assessments and continued through Week 52. Patients who completed the Induction Phase (either cohort) were enrolled into the Maintenance Phase. The maintenance treatment group assignment was based on both the Week 6 treatment response and the induction treatment assignment. At Week 6, vedolizumab-treated patients in both Cohorts 1 and 2 who had achieved clinical response (as defined by the protocol and assessed by the investigator) were randomized in a 1:1:1 ratio to one of the following blinded maintenance regimens: vedolizumab 300 mg Q4W, vedolizumab 300 mg every 8 weeks (Q8W), or placebo. These patients comprise the Maintenance ITT population, the primary efficacy population.

Patients in Induction Phase Cohorts 1 and 2 who had received vedolizumab induction treatment and had not achieved clinical response at Week 6 were assigned to receive vedolizumab every 4 weeks from Week 6 through Week 52. These patients contribute to the non-ITT population of the Maintenance Phase. Patients in Induction Phase Cohort 1 who

had been randomized to placebo were assigned to continue receiving placebo from Week 6 through Week 52. These patients also contribute to the non-ITT population of the Maintenance Phase.

Test Product, Dose and Mode of Administration: Vedolizumab drug product was supplied as a lyophilized solid formulation.

During the Induction Phase, patients randomized or assigned to vedolizumab were to receive a 300 mg dose of vedolizumab at Weeks 0 and 2. During the Maintenance Phase, patients randomized or assigned to receive vedolizumab Q4W were to receive a 300 mg dose of vedolizumab Q4W from Week 6 through Week 50 (ie, Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50). Patients randomized to receive vedolizumab Q8W during the Maintenance Phase were to receive a 300 mg dose of vedolizumab Q8W from Week 6 through Week 50 (ie, Weeks 6, 14, 22, 30, 38, and 46). In order to maintain blinding, these patients were to receive a placebo infusion (described below) at the other study visits (ie, Weeks 10, 18, 26, 34, 42, and 50).

Efficacy Assessments:

Induction

The primary efficacy assessment was the difference in the proportions of patients with clinical response at Week 6 in the vedolizumab group versus the placebo group, defined as a reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point. In addition to the primary comparisons, there were 2 secondary assessments of clinical efficacy (clinical remission and mucosal healing), which compared treatment differences between vedolizumab and placebo through formal closed testing procedures. Clinical remission was defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point and mucosal healing was defined as a Mayo endoscopic subscore of ≤ 1 point.

Maintenance

The primary efficacy assessments were the differences in the proportions of patients with clinical remission at Week 52 in the vedolizumab every 4 weeks versus placebo groups and vedolizumab every 8 weeks versus placebo groups, defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point. In addition to the primary comparisons, there were 4 key secondary assessments of clinical efficacy (durability of clinical response, mucosal healing, durability of clinical remission, and corticosteroid-free remission) which compared treatment differences between vedolizumab and placebo treatments through formal closed testing procedures. Durable clinical response was defined as clinical response at both Weeks 6 and 52; mucosal healing was defined as a Mayo endoscopic subscore of ≤ 1 point; durable clinical remission was defined as clinical remission at both Weeks 6 and 52; and corticosteroid-free remission was defined as clinical remission at Week 52 and no concomitant corticosteroids.

Pharmacokinetic, Pharmacodynamic, and HAHA Assessments:

Blood samples were drawn for serum vedolizumab levels for PK analyses prior to dosing and postdose at Weeks 0, 2, 6, 22, and 46; prior to dosing at Weeks 14 and 38; and at any time during the study visit at Weeks 4 and 52 (or early termination [ET] visit). Blood samples for serum vedolizumab levels were also collected at any unscheduled visit(s) (for assessment of disease exacerbation), at any time during the visit.

Blood samples were drawn for PD analysis at Weeks 0, 6, and 52 (or ET visit). Amendment 3 of the protocol (02 April 2009) limited the collection of PD samples to United States (US) study patients only. Pharmacodynamic samples were analyzed using the mucosal addressin cell adhesion molecule-1 (MAdCAM-1-Fc) Binding Interference Assay.

Blood samples for HAHA assessment were collected at Weeks 0, 6, 14, 26, 38, 52 (or ET visit) and 66 (or Final Safety visit). Blood samples for HAHA assessments were obtained within 30 minutes prior to dosing, if applicable. A blood sample for HAHA assessment was also collected at any unscheduled visit(s) due to disease exacerbation, at any time during the visit. Neutralizing HAHA assessments were performed for HAHA positive samples.

RESULTS

Induction Phase Disposition

A total of 895 patients were enrolled, of which 374 patients were enrolled into Cohort 1 and 521 patients were enrolled into Cohort 2. Within Cohort 1, a total of 149 patients were randomized to receive placebo and 225 patients were randomized to receive vedolizumab; all patients in the ITT population are included in the Induction Phase Safety population. There were 521 patients enrolled into Cohort 2, each of whom received open-label vedolizumab induction therapy and is included in the Induction Phase Safety population.

Induction Study Efficacy Results

At Week 6, a greater percentage of patients treated with vedolizumab achieved clinical response (47%, $P < 0.0001$) and clinical remission (17%, $P < 0.001$) compared to patients treated with placebo (26% and 5% for clinical response and remission, respectively, [Table 8](#)).

Table 8 Study C13006 Efficacy Results at Week 6 (UC Patients)

Endpoint	Placebo (N=149)	Vedolizumab (N=225)
Clinical response rate	26%	47% ($p < 0.0001$)
Clinical remission rate	5%	17% ($p < 0.001$)

Source: Study C13006 CSR, Table 14.3.1.2A (clinical response); Table 14.3.1.4A (clinical remission)

Maintenance Phase Disposition

A total of 373 vedolizumab patients had a clinical response during the Induction Phase, and were randomized to receive placebo Q4W (N = 126), vedolizumab Q8W (N = 122), or vedolizumab Q4W (N = 125) during the Maintenance Phase. Another 373 vedolizumab patients did not respond during the Induction Phase, and were assigned to receive vedolizumab Q4W during the Maintenance Phase. Patients in the Induction Study placebo

treatment group (N = 149) continued to receive placebo during the Maintenance Phase. In the ITT population, a greater proportion of patients discontinued from the placebo group (62%) than in either vedolizumab group (37% for the Q8W group and 33% for the Q4W group). In the non-ITT placebo group and the combined vedolizumab group, 80% and 52% of patients in the non-ITT placebo and combined vedolizumab groups, respectively, discontinued prematurely. The most frequent reason for discontinuation in all groups was lack of efficacy.

Maintenance Study Efficacy Results

At Week 52, a greater percentage of patients achieved clinical remission in groups treated with 300 mg Q8W (42%, P<0.0001) or Q4W (45%, P<0.0001) vedolizumab as compared to placebo (16%, [Table 9](#)). These data support the proposed Q8W dosing frequency because clinical remission rates were similar for Q8W and Q4W dosing regimens at Week 52 and more intensive dosing (Q4W) did not provide additional clinical benefit.

Table 9 Study C13006 Efficacy Results at Week 52 (UC Patients)

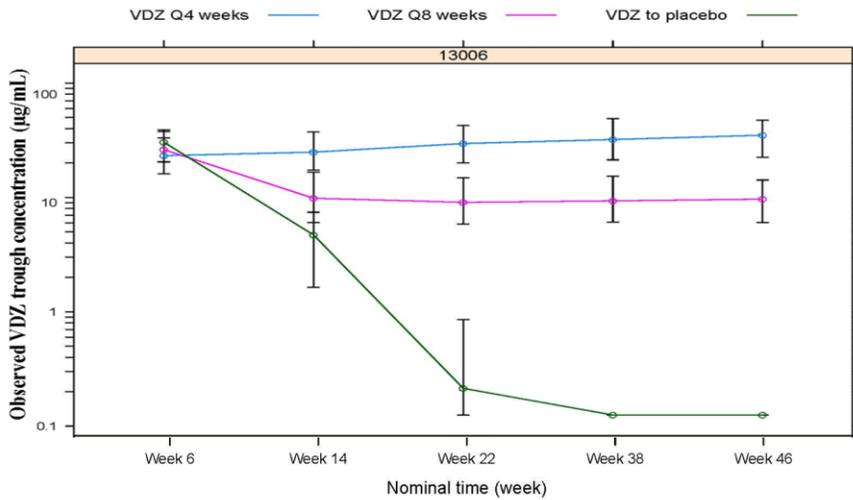
Endpoint	Placebo (N=126)	Vedolizumab Q8W (N=122)	Vedolizumab Q4W (N=125)
Clinical remission rate	16%	42% (p<0.0001)	45% (p<0.0001)

Source: Study C13006 CSR, Table 14.3.1.2AM (clinical remission)

PK Results:

In Study C13006, the administration of a loading dose of vedolizumab (Week 0 and Week 2) precludes the determination of accumulation index. As shown in **Error! Reference source not found.**, trough serum concentration was maintained at similar levels after Weeks 6 and 14 for Q4W and Q8W dose regimen, respectively.

Figure 8 Median (Interquartile Range) of Observed Serum Trough Concentration-Time Profile of Vedolizumab



Abbreviations: Q4 weeks = every 4 weeks; Q8 weeks = every eight weeks; VDZ = vedolizumab. Source: Population PK and PD Report 2012, Figure 6.

The mean (\pm SD) values of serum vedolizumab concentrations are presented in Table 10.

Table 10 Mean (\pm SD) Vedolizumab Concentrations in ITT Patients with UC from Study C13006

Patient Type	Induction Phase	Maintenance Phase	
	Trough Serum Concentration at Week 6 (μ g/mL)	Trough Serum Concentration at Week 46 (μ g/mL)	
		Q4W	Q8W
Ulcerative Colitis	26.3 (\pm 12.87) (N=210)	42.8 (\pm 28.03) (N=82)	11.2 (\pm 7.24) (N=77)

Source: Study C13006 CSR Table 14.2.1.1BM
Patients with positive ADA were excluded from this analysis

Immunogenicity Results

Patient human antihuman antibody (HAHA) status was grouped into 3 categories as follows:

- **HAHA negative subject:** a patient who did not have confirmed positive HAHA results in any post baseline sample.

- **HAHA positive subject:** a patient who had at least 1 positive HAHA result in any post baseline sample.
 - Transiently positive: defined as patients with confirmed positive HAHA in only 1 sample at a postdose visit.
 - Persistently positive: defined as patients with confirmed positive HAHA in 2 or more positive ADA samples at postdose visits.

Table 9: Immunogenicity data during maintenance phase from Study C13006 (UC) are summarized in Table 11 .

11 Summary of Human Antihuman Antibody Status – Maintenance Phase Safety Population

HAHA St
 HAHA Ne
 HAHA Po
 Transient
 Persistent
 Any Neut
 Positive
 Source: T
 Abbreviat
 vedoliz
 HAHA Ne
 HAHA Po
 Transient
 Persistent
 Neutralizi
 Proportion
 a Patients
 b Patients
 c Patient
 weeks q
 Neutralizi
 Proportion
 a Patient

As mentioned in the clinical pharmacology review, the immunogenicity of vedolizumab during treatment could not be reliably assessed due to drug interference issue in the immunogenicity assay. The incidence rate was reported as 20% (25/126) in VDZ/PBO subjects compared to 4% (23/620) in VDZ/VDZ subjects. Please refer to section 2.3.3 of the QBR review for more information related to the immunogenicity incidence rate and the impact of immunogenicity on PK, efficacy and safety.

C13007

Study Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Crohn’s Disease

Study Objectives:

Induction Phase

- To determine the effect of vedolizumab induction treatment on clinical remission at 6 weeks
- To determine the effect of vedolizumab induction treatment on enhanced clinical response at 6 weeks
- To determine the effect of vedolizumab induction treatment on serum C-reactive protein (CRP) levels at 6 weeks in patients with elevated CRP levels at baseline

Maintenance Phase

- To determine the effect of vedolizumab maintenance treatment on clinical remission at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on enhanced clinical response at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on corticosteroid-free remission at 52 weeks
- To determine the effect of vedolizumab maintenance treatment on durability of clinical Remission

METHODS

Design: This phase 3, randomized, blinded, placebo-controlled study in patients with moderately to severely active CD comprises 2 phases (refer to Figure 9).

Specifically, “Induction Study” refers to the placebo-controlled formal, planned induction efficacy analyses of the effects of vedolizumab administered at Weeks 0 and 2;

“Maintenance Study” refers to the placebo-controlled formal, planned maintenance efficacy analyses of vedolizumab administered as maintenance therapy in patients who had achieved clinical response during induction.

As shown in Figure 9, the Induction Phase began at Week 0, included study drug dosing at Weeks 0 and 2, and concluded with induction-related assessments at Week 6. Patients who completed the Induction Phase were to enter into the Maintenance Phase, which began at Week 6, included study drug dosing at Week 6 and every 4 weeks (Q4W) or every 8 weeks (Q8W) thereafter, and concluded with Week 52 assessments.

Figure 9 Treatment Phases, Study Drug Randomization, and Treatment Assignment Schema

Test Product, Dose and Mode of Administration: Vedolizumab drug product was supplied as a lyophilized solid formulation.

During the Induction Phase, patients randomized or assigned to vedolizumab were to receive a 300 mg dose of vedolizumab at Weeks 0 and 2. During the Maintenance Phase, patients randomized or assigned to receive vedolizumab Q4W were to receive a 300 mg dose of vedolizumab Q4W from Week 6 through Week 50 (ie, Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50). Patients randomized to receive vedolizumab Q8W during the Maintenance Phase were to receive a 300 mg dose of vedolizumab Q8W from Week 6 through Week 50 (ie, Weeks 6, 14, 22, 30, 38, and 46). In order to maintain blinding, these patients were to receive a placebo infusion (described below) at the other study visits (ie, Weeks 10, 18, 26, 34, 42, and 50).

Pharmacokinetic, Pharmacodynamic, and HAHA Assessments:

Blood samples were drawn for serum vedolizumab levels for PK analyses prior to dosing and postdose at Weeks 0, 2, 6, 22, and 46; prior to dosing at Weeks 14 and 38; and at any time during the study visit at Weeks 4 and 52 (or early termination [ET] visit). Blood samples for serum vedolizumab levels were also collected at any unscheduled visit(s) (for assessment of disease exacerbation), at any time during the visit.

Blood samples were drawn for PD analysis at Weeks 0, 6, and 52 (or ET visit). Amendment 3 of the protocol (02 April 2009) limited the collection of PD samples to United States (US) study patients only. Pharmacodynamic samples were analyzed using the mucosal addressin cell adhesion molecule-1 (MAdCAM-1-Fc) Binding Interference Assay.

Blood samples for HAHA assessment were collected at Weeks 0, 6, 14, 26, 38, 52 (or ET visit) and 66 (or Final Safety visit). Blood samples for HAHA assessments were obtained within 30 minutes prior to dosing, if applicable. A blood sample for HAHA assessment was also collected at any unscheduled visit(s) due to disease exacerbation, at any time during the visit. Neutralizing HAHA assessments were performed for HAHA positive samples.

RESULTS

Induction Phase Disposition

A total of 1115 patients were enrolled and dosed, of whom 368 patients were enrolled into Cohort 1 (ITT Population) and 747 patients were enrolled into Cohort 2. Within Cohort 1, a total of 148 patients were randomized to receive placebo and 220 patients were randomized to receive vedolizumab. There were 747 patients enrolled into Cohort 2, each of whom received open-label vedolizumab induction therapy and is included in the Induction Phase Safety Population. Overall, baseline demographic characteristics were similar for the treatment groups in the Induction Study ITT Population.

Induction Study Efficacy Results

For the two primary endpoints at Week 6 (Table 12), a higher percentage of patients treated with vedolizumab achieved clinical remission (15%, $p < 0.025$) as compared to placebo (7%); however, the difference in the percentage of patients who demonstrated enhanced clinical response was not statistically significant (31% and 26% for VDZ and placebo, respectively).

Table 12 Efficacy Results for Study C13007 at Week 6 (CD Patients)

Endpoint	Placebo (N=148)	Vedolizumab (N=220)
Clinical remission rate	7%	15% ($p < 0.025$)
Enhanced clinical response rate	26%	31%

Source: Study C13007 CSR, Table 14.3.1.2A and Table 14.3.1.4A

Maintenance Phase Disposition

A total of 461 vedolizumab patients had a clinical response during the Induction Phase, and were randomized to receive placebo (N = 153), vedolizumab Q8W (N = 154), or vedolizumab Q4W (N = 154) during the Maintenance Phase. Another 506 vedolizumab patients did not respond during the Induction Phase, and were assigned to receive vedolizumab Q4W during the Maintenance Phase. Patients in the Induction Study placebo treatment group (N = 148) continued to receive placebo during the Maintenance Phase. In the ITT population, a greater proportion of patients discontinued from the placebo group (58%) than in either vedolizumab group (53% for the Q8W group and 47% for the Q4W group). In the non-ITT placebo group and the combined vedolizumab group, 72% and 61% of patients, respectively, discontinued prematurely. The most frequent reason for discontinuation in all groups was lack of efficacy. In the Maintenance Study ITT Population, the demographic characteristics were generally similar among the treatment groups, except for geographic region.

Maintenance Study Efficacy Results

At Week 52, a greater percentage of patients achieved clinical remission in groups treated with 300 mg Q8W (39%, $P < 0.001$) or Q4W (36%, $P < 0.01$) vedolizumab as compared to placebo (22%, Table 13). These data support the proposed Q8W dosing frequency because clinical remission rates were similar for Q8W and Q4W dosing regimens at Week 52 and more intensive dosing (Q4W) did not provide additional clinical benefit.

Table 13 Efficacy Results for Study C13007 at Week 52 (CD Patients)

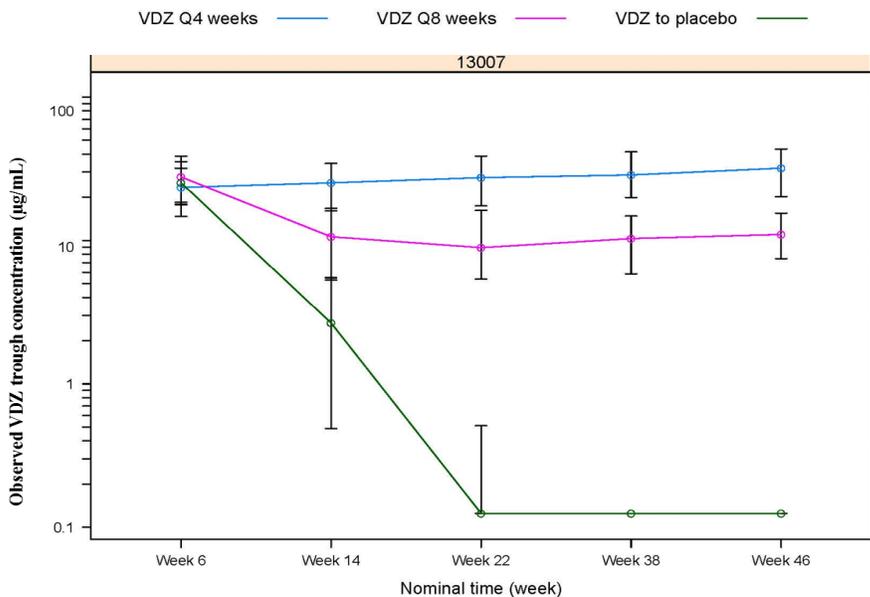
Endpoint	Placebo (N=153)	Vedolizumab Q8W (N=154)	Vedolizumab Q4W (N=154)
Clinical remission rate	22%	39% ($p < 0.001$)	36% ($p < 0.01$)

Source: Study C13007 CSR, Table 14.3.1.2AM (clinical remission)

PK Results:

In Study C13007, the administration of a loading dose of vedolizumab (Week 0 and Week 2) precludes the determination of accumulation index. As shown in Figure 10, trough serum concentration was maintained at similar levels after Weeks 6 and 14 for Q4W and Q8W dose regimen, respectively.

Figure 10 Median (Interquartile Range) of Observed Serum Trough Concentration-Time Profile of Vedolizumab



Abbreviations: Q4 weeks = every 4 weeks; Q8 weeks = every eight weeks; VDZ = vedolizumab.

Source: Population PK and PD Report 2012, Figure 7.

The mean (\pm SD) values of serum vedolizumab concentrations are presented in Table 14.

Table 14 Mean (\pm SD) Vedolizumab Concentrations in ITT Patients with CD from Study C13007

Patient Type	Induction Phase	Maintenance Phase	
	Trough Serum Concentration at Week 6 (μ g/mL)	Trough Serum Concentration at Week 46 (μ g/mL)	
		Q4W	Q8W
Crohn's Disease	27.4 (\pm 19.17) (N=198)	32.5 (\pm 18.42) (N=84)	13.0 (\pm 9.08) (N=72)

Source: Study C13007 CSR Table 14.2.1.1AM
Patients with positive ADA were excluded from this analysis

Immunogenicity Results

Patient human antihuman antibody (HAHA) status was grouped into 3 categories as follows:

- **HAHA negative subject:** a patient who did not have confirmed positive HAHA results in any post baseline sample.
- **HAHA positive subject:** a patient who had at least 1 positive HAHA result in any post baseline sample.
 - Transiently positive: defined as patients with confirmed positive HAHA in only 1 sample at a postdose visit.
 - Persistently positive: defined as patients with confirmed positive HAHA in 2 or more positive ADA samples at postdose visits.

Table 9:

immunogenicity data during maintenance phase from Study C13007 (CD) are summarized in Table 15.

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15 Summary of Human Antihuman Antibody Status – Maintenance Phase Safety Population

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b Patient
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weeks c
Neutralizi
Proportion
a Patient
b Patient
c Patient
weeks c

Similar to the results of Study C13006, the incidence rate was reported as 13% (20/153) in VDZ/PBO subjects compared to 4% (33/814) in VDZ/VDZ subjects. Please refer to section 2.3.3 of the QBR review for more information related to the immunogenicity incidence rate and the impact of immunogenicity on PK, efficacy and safety.

C13011

Study Title: A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's Disease

Study Objectives:

Primary Objective

- To determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the subgroup of patients defined as having failed tumor necrosis factor alpha (TNF α) antagonist therapy (TNF α antagonist failure subpopulation)

Secondary Objectives

- To determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in the entire study population
- To determine the effect of vedolizumab induction treatment on clinical remission at Week 10 in the TNF α antagonist failure subpopulation and in the entire study population
- To determine the effect of vedolizumab induction treatment on sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) in the TNF α antagonist failure subpopulation and in the entire study population
- To determine the effect of vedolizumab induction treatment on enhanced clinical response at Week 6 in the TNF α antagonist failure subpopulation

METHODS

Design: This phase 3, multinational, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of vedolizumab for the induction of clinical response and remission in patients with moderately to severely active CD. Of the total patients enrolled, 75% were to have previously failed TNF α antagonist therapy and 25% were to have been naïve to TNF α antagonist therapy. Patients were randomized 1:1 to receive either vedolizumab or placebo at Weeks 0, 2, and 6. The randomization to treatment assignment was stratified by the presence or absence of each of the following: 1) previous failure of TNF α antagonist therapy or naïve to TNF α antagonist therapy, 2) concomitant use of oral corticosteroids, and 3) concomitant use of immunomodulators (6-mercaptopurine [6-MP], azathioprine, or methotrexate).

Pharmacokinetic Assessments:

Blood samples were drawn for determination of vedolizumab serum concentrations in all patients postdose at Week 0, prior to dosing and postdose at Week 6, at any time during the study visit at Week 10 (or ET visit), and at any unscheduled visit(s) due to disease exacerbation. Postdose PK samples were to be obtained as close to the end of infusion as feasible and must have been within 2 hours after the start of the infusion.

RESULTS

In the overall patient population, 207 patients were randomized to receive placebo and 209 patients were randomized to receive vedolizumab. In both treatment groups, all randomized patients received at least 1 dose of blinded study drug and were included in the Overall Safety and ITT Populations. Among the 315 TNF α antagonist failure patients, 157 received placebo and 158 received vedolizumab; each of these patients was included in the TNF α Antagonist Failure Safety and ITT Subpopulations.

Efficacy Results

For the analysis of the primary endpoint, no statistically significant difference was observed between the vedolizumab (15.2%) and placebo (12.1%) groups for the proportions of patients in clinical remission at Week 6 in the TNF α Antagonist Failure ITT Subpopulation. The treatment difference from placebo was 3.0% (95% CI -4.5, 10.5; $p = 0.4332$), with a relative probability of achieving clinical remission at Week 6 of 1.2 (relative risk with 95% CI 0.7, 2.2).

Since the primary efficacy endpoint did not reach statistical significance, only descriptive summaries are provided for the ranked secondary endpoints. The proportions of patients in each treatment group who achieved the secondary endpoints are presented.

- Proportion of patients in clinical remission at Week 6 in the Overall ITT Population (19.1% of vedolizumab-treated patients and 12.1% of placebo-treated patients; the treatment difference from placebo was 6.9%).
- Proportion of patients in clinical remission at Week 10 in the TNF α Antagonist Failure ITT Subpopulation (26.6% of vedolizumab-treated patients and 12.1% of placebo-treated patients; the treatment difference from placebo was 14.4%) and in the Overall ITT Population (28.7% of vedolizumab-treated patients and 13.0% of placebo-treated patients; the treatment difference from placebo was 15.5%).
- Proportion of patients with sustained clinical remission (ie, clinical remission at both Week 6 and Week 10) in the TNF α Antagonist Failure ITT Subpopulation (12.0% of vedolizumab-treated patients and 8.3% of placebo-treated patients; the treatment difference from placebo was 3.7%) and in the Overall ITT Population (15.3% of vedolizumab-treated patients and 8.2% of placebo-treated patients; the treatment difference from placebo was 7.0%).
- Proportion of patients with enhanced clinical response at Week 6 in the TNF α Antagonist Failure ITT Subpopulation (39.2% of vedolizumab-treated patients and 22.3% of placebo-treated patients; the treatment difference from placebo was 16.9%).

Results from the ranked secondary endpoints suggest that a potential treatment benefit for vedolizumab in the TNF α Antagonist Failure ITT Subpopulation may be achieved beyond the 6-week treatment and evaluation period used to evaluate the primary endpoint. In the Overall ITT Population, treatment differences for clinical remission at Week 6, clinical remission at Week 10, and enhanced clinical response at Week 6 were greater for vedolizumab patients than placebo patients.

Because of the short treatment duration, the PK and immunogenicity data were not relevant to guide the chronic treatment and thus not presented in this review.

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/s/

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	125476
Original Submission Dates	06/20/2013
PDUFA Due Date	02/18/2014
Brand Name	Entyvio
Generic Name	Vedolizumab
Primary Clinical Pharmacology Reviewer	Lanyan Fang, Ph.D.
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Pharmacogenomics Team Leader	Michael Pacanowski, Pharm.D.
OCP Division	DCP III
OND Division	DGIEP
Sponsor	Takeda Pharmaceuticals
Relevant IND(s)	9125
Submission Type	NME
Formulation; Strength(s)	300 mg of lyophilized powder in a single-use vial
Proposed indication	Adult ulcerative colitis (UC) and Crohn’s disease (CD)
Proposed Dosage and Administration	300 mg infused intravenously over approximately 30 minutes at Weeks zero, two and six, then every eight weeks (Q8W) thereafter.

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1. EXECUTIVE SUMMARY

This is an original BLA for vedolizumab (VDZ or MLN0002), a new molecular entity (NME), which is a humanized monoclonal antibody. Vedolizumab is thought to selectively bind to the $\alpha_4\beta_7$ integrin on pathogenic gut-homing lymphocytes and inhibits adhesion of these cells to mucosal addressin cell adhesion molecule 1 (MAdCAM 1), but not vascular cell adhesion molecule 1 (VCAM 1). The proposed indication is for the treatment of moderately to severely active Crohn's disease (CD) and ulcerative colitis (UC) in adult patients who have 1) had an inadequate response with, 2) lost response to, or 3) were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF α) antagonist.

The proposed dosage form is a lyophilized cake available in sterile single-use vials containing 300 mg of vedolizumab for intravenous use. The intended commercial product of vedolizumab was used throughout the phase 3 clinical trials.

A total of 19 clinical studies have been conducted, of which 7 were phase 1 studies conducted in healthy subjects, 8 were phase 1b/2 studies conducted in patients with UC or CD, and 4 were phase 3 studies (C13006, C13007, C13011 and C13008 [currently ongoing]) conducted in patients with UC or CD. The proposed dosing regimen is: 300 mg administered as a 30-minute intravenous infusion at weeks zero, two and six and then every eight weeks (Q8W) thereafter. The proposed dosing regimen was examined in the Phase 3 trials and these data formed the basis to support the proposed indications.

1.1 Recommendation

From a clinical pharmacology perspective, the information submitted to support this BLA is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post-Marketing Requirements

There are no post-marketing requirements for this submission.

1.3 Post-Marketing Commitments

The Clinical Pharmacology review team recommends the following post marketing commitment (PMC) studies:

- A study to develop and qualify an anti-drug antibody (ADA) assay that could tolerate therapeutic vedolizumab concentrations. This recommendation is based on that ADA signal could be reduced or undetectable using the current assay as vedolizumab steady state trough concentration (~11 $\mu\text{g/mL}$) at the proposed dose regimen (i.e.,

300 mg at Week 0, 2, 6 and Q8W thereafter) is about 20-fold higher than the ADA assay drug tolerance level (500 ng/mL). Please refer to section 2.6 for more details.

- 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. Preferably, ADA impact on PK and efficacy should be assessed once the reanalysis of immunogenicity samples is complete because the impact of ADA could not be reliably assessed in the current BLA submission but data in a small number of subjects suggest ADA may have negative impact on PK and efficacy. As stated in section 2.3.4.4 and 2.3.4.4, persistent ADA had significant impact on vedolizumab PK (reduced or undetectable vedolizumab concentrations) and efficacy (none of subjects with persistent ADA achieved clinical remission at either Weeks 6 or 52). It was noted that 4 subjects with transient ADA also had significantly reduced (<1 µg/mL, N=2) or undetectable (N=2) vedolizumab concentrations at Week 6. Therefore, we are concerned that some of the subjects classified as transient ADA based on the current ADA assay could be misclassified and the impact assessment maybe inadequate.
- 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.

1.4 Summary of Clinical Pharmacology Findings

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

Pharmacokinetics (PK)

- Vedolizumab exhibits target-mediated drug disposition (Figure 13); hence, clearance decreases with increasing concentration due to target saturation at higher concentrations. The dose-normalized concentration-time profiles were similar for

300 and 600 mg after a single dose IV infusion, suggesting the saturation of the nonlinear clearance pathway at these doses and the linear clearance pathway is dominant. The serum half-life of vedolizumab was estimated to be approximately 18 to 21 days following 300 or 600 mg administration using non-compartmental analysis (Table 14).

- No apparent differences were observed in vedolizumab PK in subjects with UC or CD based on the trough concentrations at Week 6 and at steady state during maintenance phase (Table 16). Additionally, the clearance of the linear pathway (CL_L) for subjects with UC and CD was estimated as 0.159 L/day and 0.155 L/day, respectively, based on a population PK analysis (Table 15) in which the K_m and V_{max} of the nonlinear elimination pathway were predefined to be the same value for subjects with UC and CD. The population PK analysis results showed no clinically meaningful impact on PK for the following covariates: severity of disease state, body weight, serum albumin, prior treatment with TNF α antagonist therapy, age (18-78 years) and co-administered medications.

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

The relationship between vedolizumab serum concentration and the extent of $\alpha_4\beta_7$ binding saturation was assessed based on data from MAdCAM-1-Fc biomarker (Study C13002). Maximum $\alpha_4\beta_7$ binding saturation (i.e., ~ 100% inhibition of MAdCAM-1-Fc binding to $\alpha_4\beta_7$) was achieved within one hour following the first vedolizumab dose at all dose levels ranging from 2 to 10 mg/kg in subjects with UC (Figure 2), i.e., the maximum $\alpha_4\beta_7$ inhibition has no relationship with dose. The maximum inhibition remained throughout the whole treatment period until 84, 126 and 112 days after the last dose (at Day 85) for the 2, 6 and 10 mg/kg dose cohorts, respectively. Of note, the corresponding observed mean vedolizumab concentrations at the time of loss of near-maximal $\alpha_4\beta_7$ inhibition were approximately 2 - 6 $\mu\text{g/mL}$ (Table 10).

Given the proposed dosing regimen (300 mg Q8W, i.e., ~ 4 mg/kg Q8W), near-maximum $\alpha_4\beta_7$ binding would be maintained during the entire dosing interval for the majority of subjects receiving the proposed 300 mg Q8W (mean trough ~10 $\mu\text{g/mL}$) dosing regimen.

Disease-Drug-Drug Interactions (DDDI)

The applicant didn't assess the potential of vedolizumab to impact the PK of other co-administered drugs. As UC and CD involve chronic inflammation and are associated with an imbalanced cytokine network, indirect impacts on the formation of CYP450 enzymes cannot be ruled out. Therefore, the potential exists for an improvement in the inflammatory disease condition upon treatment with vedolizumab, to indirectly impact the expression of CYP450 enzymes. So, the applicant needs to evaluate the DDDI potential between vedolizumab and other CYP substrates which may be co-administered with vedolizumab, in the UC and CD population.

Efficacy Results from Pivotal Phase 3 Trials

UC: The efficacy of vedolizumab for the treatment of adult patients with moderately to severely active UC (Mayo score 6 to 12 with endoscopic subscore ≥ 2) was demonstrated in a randomized, double-blind, placebo-controlled trial evaluating efficacy endpoints at Week 6 and Week 52 (C13006). At Week 6, a greater percentage of patients treated with vedolizumab achieved clinical response (47%, $P < 0.0001$) and clinical remission (17%, $P < 0.001$) compared to patients treated with placebo (26% and 5% for clinical response and remission, respectively, Table 4). At Week 52, a greater percentage of patients achieved clinical remission in groups treated with 300 mg Q8W (42%, $P < 0.0001$) or Q4W (45%, $P < 0.0001$) vedolizumab as compared to placebo (16%, Table 5). These data support the proposed Q8W dosing frequency because clinical remission rates were similar for the Q8W and Q4W dosing regimens at Week 52 and the more intensive dosing regimen (Q4W) did not provide additional clinical benefit.

CD: The efficacy of vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450) was evaluated in a randomized, double-blind, placebo-controlled trial which evaluated efficacy endpoints at Week 6 and Week 52 (C13007). For the two primary endpoints at Week 6, a higher percentage of patients treated with vedolizumab achieved clinical remission (15%, $p < 0.025$) as compared to placebo (7%); however, the difference in the percentage of patients who demonstrated enhanced clinical response was not statistically significant (31% and 26% for VDZ and placebo, respectively, Table 8).

At Week 52, a greater percentage of patients achieved clinical remission in groups treated with 300 mg Q8W (39%, $P < 0.001$) or Q4W (36%, $P < 0.01$) vedolizumab as compared to placebo (22%, Table 9). These data support the proposed Q8W dosing frequency because clinical remission rates were similar for the Q8W and Q4W dosing regimens at Week 52 and the more intensive dosing regimen (Q4W) did not provide additional clinical benefit.

Exposure-Response Relationship

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

CD: Based on univariate and multivariate logistic regression analyses, no exposure-response was evident for the probability of clinical remission or enhanced clinical response as a function of mean trough concentrations. This was consistent with the lack of dose-response

observed between the Q4W and Q8W dosing regimens at Week 52. Thus, the applicant's proposal for the Q8W dosing regimen is acceptable.

Immunogenicity

- The immunogenicity of vedolizumab during treatment could not be reliably assessed due to the drug interference issue in the immunogenicity assay. Specifically, the mean vedolizumab steady-state trough concentrations for the 300 mg Q8W and Q4W regimens were approximately 10 and 30 µg/mL, respectively (Table 16). These levels were significantly greater than the drug tolerance level (i.e., 500 ng/mL) of the immunogenicity assay (refer to section 2.6). Therefore, the incidence rate determined during treatment phase is expected to be under-estimated.
- Based on data from Phase 3 Studies (C13006 and C13007), 56 of 1434 (4%) subjects who received continuous vedolizumab treatment in the maintenance phase (i.e., subjects who received VDZ in both induction and maintenance phase, VDZ/VDZ) developed anti-vedolizumab antibody (ADA) at any time during treatment. Nine of 56 subjects were persistently positive (positive ADA at two or more study visits) and 33 of 56 subjects developed neutralizing antibodies (Table 20). Due to the aforementioned drug interference issue, the applicant-reported incidence rate of 4% is an underestimation.
- In subjects who received VDZ in the induction phase and placebo in the maintenance phase (VDZ/PBO), the immunogenicity incidence rate was 17% (20/117) at Week 52 (Table 21) when vedolizumab levels were undetectable and no drug interference issue was expected. However, since ADA could degrade during the long washout period, the incidence rate of 17% could still be an underestimation.
- ADA appeared to have affected the PK of vedolizumab. Six subjects with persistent ADA and available vedolizumab concentration data, all had a substantial decrease in their serum concentrations of vedolizumab, either to undetectable (N=5) or negligible levels (N=1) at Weeks 6 and 52 (refer to section 2.3.4.2).
- While the small number of ADA positive subjects precluded definitive conclusions regarding the impact of immunogenicity on the overall efficacy and safety in the phase 3 studies, none of the eight subjects with persistently positive ADA achieved clinical remission at Weeks 6 or 52 (refer to section 2.3.4.4).

2. QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Vedolizumab is a recombinant humanized, immunoglobulin G₁ (IgG₁), monoclonal antibody (mAb) directed against the human lymphocyte integrin $\alpha_4\beta_7$ and is being developed for the

treatment of ulcerative colitis (UC) and Crohn's disease (CD). The molecular weight is approximately 146 KDa.

Vedolizumab is composed of 2 light chains of the kappa subclass and 2 heavy chains linked together by 2 disulfide bridges to form a Y-shaped molecule (Figure 1). (b) (4)



(b) (4)

Formulation (Drug Product)

The vedolizumab drug product (DP) is a lyophilized formulation. Reconstituted vedolizumab drug product contains (b) (4) vedolizumab (b) (4) (b) (4) L-histidine (b) (4) L-histidine monohydrochloride (b) (4) (b) (4) L-arginine hydrochloride (b) (4) sucrose, and (b) (4) polysorbate 80. Vedolizumab drug product is reconstituted with sterile water for injection.

Reviewer's comment: MLN0002 (Process C) was the formulation used in all phase 3 clinical trials (C13006, C13007, C13008, and C13011) and is the intended commercial product. PK comparability between Process B and C was assessed in Study C13009 and appeared comparable. Vedolizumab PK characteristics were well characterized in studies with Process B or C drug products. Additional PK data from studies with Process A (comparability to Process B or C is unknown) would not add value to the overall assessment of vedolizumab, therefore, studies conducted in healthy and subjects with UC or CD using Process B or C drug products were the focus of the current review.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Mechanism of Action

Vedolizumab is a recombinant humanized IgG1 antibody. It is thought to selectively bind $\alpha_4\beta_7$ integrin, which is a glycoprotein present on the surface of certain populations of leukocytes involved in gastrointestinal (GI) mucosal immunity. The ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1) is preferentially expressed on gastrointestinal mucosa-associated endothelium. The binding of $\alpha_4\beta_7$ integrin to its natural ligand MAdCAM-1 mediates migration of leukocytes into the GI mucosa and associated lymphoid tissue. When MLN0002 binds $\alpha_4\beta_7$ integrin found on the surface of these particular leukocytes, it prevents the interaction of $\alpha_4\beta_7$ -MAdCAM-1. Thus, blocking of $\alpha_4\beta_7$ integrin by Vedolizumab is thought to prevent the migration of these leukocytes into the GI mucosa. Inhibiting the migration of these leukocytes to the GI tract is thought to decrease the pathological inflammation associated with CD and UC.

Proposed Therapeutic Indications

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

2.1.3 What are the proposed dose regimen and routes of administration?

Vedolizumab is intended to be administered as an intravenous infusion over 30 minutes. The recommended dose of vedolizumab is 300 mg administered at 0, 2 and 6 weeks and then every 8 weeks thereafter.

The treatment schedule is the same for both UC and CD.

The applicant proposed that some patients who have experienced lack of response or a decrease in their response may receive an increase in dosing frequency to 300 mg vedolizumab every 4 weeks (Q4W). Furthermore, the applicant proposed that continuation of therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit by Week 14.

2.1.4 What drugs (substances, products) indicated for the same indication are approved in the United States (US)?

The drugs which are conventional pharmacologic treatment and approved for treatment of UC and CD in the United States (US) are:

- Corticosteroids
- 5-aminosalicylates (5-ASAs)

The following drugs are also used as standard of care for the treatment of UC and CD in the US:

- Thiopurines
- Cyclosporine
- Methotrexate

In the US, there are currently 3 biologic therapeutics approved for treatment of UC and 4 for CD, as summarized in Table 1.

Table 1 **Biologics Currently Approved in the US for Treatment of Ulcerative Colitis or Crohn’s Disease**

Name	Type of antibody	MOA	Commercial name	Indication
Infliximab	Chimeric	Directed against TNF α	REMICADE [®]	UC, CD,
Adalimumab	Human	Directed against TNF α	HUMIRA [®]	UC, CD,
Certolizumab pegol	Humanized, pegylated	Directed against TNF α	CIMZIA [®]	CD
Golimumab	Human	Directed against TNF α	SIMPONI [®]	UC
Natalizumab	Human	integrin antagonist (pan-a4)	TYSABRI [®]	CD

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Table 2 summarizes the vedolizumab clinical pharmacology and biopharmaceutics studies and the clinical studies used to support the dosing recommendations.

Table 2 Clinical Studies in Healthy Subjects and Subjects With Ulcerative Colitis and Crohn’s Disease

Study No.	Study Design	Manufacturing Process Dosing Regimen Dose Route	Number of Subjects Enrolled
C13001	Phase 1, double-blind, single ascending dose, randomized, placebo-controlled study. Healthy subjects, 18-65 yrs	Product B Single dose 0.2 mg/kg IV (n = 8) 0.5 mg/kg IV (n = 7) 2 mg/kg IV (n = 8) 6 mg/kg IV (n = 8) 10 mg/kg IV (n = 8) Placebo IV (n = 10)	Total = 49 VDZ = 39 Placebo = 10
C13005	Phase 1, single dose Healthy subjects with low and high body weights, 18-65 yrs	Product B Single dose 6 mg/kg IV (n = 26)	Total = 26 VDZ = 26
C13009	Phase 1, single dose to evaluate PK, PD, safety & tolerability of Process C drug product Healthy subjects, 18-45 yrs	Product B & C Single dose 300 mg IV, Process C (n=13) 600 mg IV, Process C (n=26) 600 mg IV, Process B (n=23) Placebo	Total = 87 VDZ = 62 Placebo = 25
C13012	Phase 1, effects of MLN0002 on the CD4 ⁺ :CD8 ⁺ lymphocyte ratio in cerebrospinal fluid healthy volunteers 18-45 yrs	Process C Single dose 450 mg IV	Total = 14 VDZ = 14
C13002	Phase 2, randomized, double-blind, placebo-controlled, PK/PD, multiple-dose, multicenter study. Mild to moderately severe UC, 18-70 yrs	Product B 4 doses (Days 1, 14, 29 and 85) 2 mg/kg IV (n = 13) 6 mg/kg IV (n = 14) 10 mg/kg IV (n = 11) Placebo IV (n = 9)	Total = 47 VDZ = 38 Placebo = 9
C13006	Phase 3, randomized, placebo-controlled, multicenter, blinded trial of induction & maintenance moderate to severe UC 18-80 yrs	Process C Multiple dose Induction (Weeks 0 and 2): <ul style="list-style-type: none"> • 300 mg IV • Placebo Maintenance (for 44 weeks): <ul style="list-style-type: none"> • 300 mg IV Q4W • 300 mg IV Q8W • Placebo 	Induction (wks 0-2): <u>ITT:</u> VDZ = 225 Placebo = 149 <u>Non-ITT:</u> VDZ = 521 Maintenance (wks 6-50): <u>ITT:</u> VDZ Q4W = 125 VDZ Q8W = 122 Placebo = 126 <u>Non-ITT:</u> VDZ Q4W = 373 Placebo = 149

C13007	Phase 3, randomized, placebo-controlled, multicenter, blinded trial of induction & maintenance moderate to severe CD 18-80 yrs	Process C Multiple dose Induction (Weeks 0 and 2): <ul style="list-style-type: none"> • 300 mg IV • Placebo Maintenance (for 44 weeks): <ul style="list-style-type: none"> • 300 mg IV Q4W • 300 mg IV Q8W • Placebo 	Induction Phase: <u>ITT:</u> VDZ = 220 Placebo = 148 <u>Non-ITT:</u> VDZ = 747 Maintenance Phase: <u>ITT:</u> VDZ Q4W = 154 VDZ Q8W = 154 Placebo = 153 <u>Non-ITT:</u> VDZ Q4W = 506 Placebo = 148
C13011	Phase 3, randomized, placebo-controlled, multicenter, blinded trial of induction Patients with moderate to severe CD who have failed TNF α antagonist therapy 18-80 yrs	Process C Induction (wks 0, 2, and 6) 300 mg IV (n=198) Placebo (n=198)	<u>ITT:</u> VDZ = 209 Placebo = 207

Additional study design features of the pivotal Phase 3 studies were summarized below.

Study C13006 (UC)

Study C13006 was a randomized, double-blind, placebo-controlled trial evaluating efficacy endpoints at Week 6 and Week 52. The study population was adult patients with moderately to severely active UC (Mayo score 6 to 12 with endoscopic subscore ≥ 2). Enrolled patients had failed at least one conventional therapy, including corticosteroids, immunomodulators and/or a TNF α antagonist. Two cohorts of patients received vedolizumab at Week 0 and Week 2: Cohort 1 patients were randomized to receive either vedolizumab 300 mg or placebo in a double-blind fashion, and Cohort 2 patients were treated with open-label vedolizumab 300 mg at Week 0 and Week 2.

The evaluation of efficacy at Week 6 was based on 374 patients in Cohort 1 who were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo at Week 0 and Week 2.

The evaluation of efficacy at Week 52 was based on 373 vedolizumab treated patients from Cohort 1 and 2 who had achieved clinical response at Week 6 and were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks or placebo every four weeks.

Study C13007 (CD)

Study C13007 was a randomized, double-blind, placebo-controlled trial evaluating efficacy endpoints at Week 6 and Week 52. The study population was adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450) for both induction and maintenance phase. Enrolled patients had failed at least one

conventional therapy, including corticosteroids, immunomodulators and/or one or more TNF α antagonists. Two cohorts of patients received vedolizumab at Week 0 and Week 2: Cohort 1 patients were randomized to receive either vedolizumab 300 mg or placebo in a double-blind fashion, and Cohort 2 patients were treated with open-label vedolizumab 300 mg at Week 0 and Week 2.

The evaluation of efficacy at Week 6 was based on 368 patients who were randomized in a double-blind fashion (3:2) to receive two doses of vedolizumab 300 mg or placebo at Week 0 and Week 2.

The evaluation of efficacy at Week 52 was based, 461 vedolizumab treated patients from Cohorts 1 and 2 who had achieved clinical response (defined as a ≥ 70 -point decrease in CDAI score from baseline) at Week 6 and were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks or placebo every four weeks.

Study C13011 (CD)

Study C13011 was a second randomized, double-blind, placebo-controlled trial that evaluated efficacy at Week 6 (primary) following vedolizumab administration at Weeks 0 and 2 and efficacy at Week 10 (secondary) following vedolizumab administration at Weeks 0, 2 and 6. A total of 416 patients were randomized in a double-blind fashion (1:1) to receive either vedolizumab 300 mg or placebo at Weeks 0, 2 and 6. Approximately 75% of enrolled patients have failed at least one conventional therapy and one or more TNF α antagonist therapies. The remainder patients have failed at least one conventional therapy and are naïve to TNF α antagonist therapies.

2.2.2 What is the basis for selecting the response endpoints and what are the efficacy outcomes in pivotal clinical studies?

Ulcerative Colitis

The primary efficacy endpoint in the pivotal Phase 3 study (C13006) was based on complete Mayo score which is a standard assessment tool of disease activity in the clinical studies with UC. Mayo score is a composite index of 4 disease activity variables (stool frequency, rectal bleeding, findings on sigmoidoscopy, and physician’s global assessment); each disease activity variable was scored on a scale from 0 to 3 (higher scores indicate greater disease activity). The efficacy endpoints used in the phase 3 study for subjects with UC (C13006) are presented in Table 3.

Table 3 Study C13006 Primary Efficacy Endpoints

	Primary efficacy endpoints
Induction Phase	<ul style="list-style-type: none"> Clinical response at Week 6: Reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ decrease from baseline, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.

Maintenance Phase	<ul style="list-style-type: none"> Clinical remission at Week 52: Complete Mayo score of ≤ 2 points and no individual subscore > 1 point.
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Biomarker: Fecal Calprotectin

Fecal calprotectin is a neutrophil granule protein released during an inflammatory response. Calprotectin released into the feces after neutrophil recruitment appeared to be correlated with inflammation in the intestine. Fecal calprotectin in a healthy individual is $< 50 \mu\text{g/g}$. Levels over $50 \mu\text{g/g}$ are indicative of increased inflammation, and moderate to severe IBD is associated with levels greater than $500 \mu\text{g/g}$ stool. Fecal calprotectin was determined by quantitative enzyme-linked immunosorbent assay.

Reviewer's comment: Fecal calprotectin is highly variable, nonspecific and usually considered as an exploratory biomarker. Therefore, fecal calprotectin is not a validated biomarker for measuring the response to treatment in subjects with UC.

Efficacy Results: The efficacy of vedolizumab for the treatment of adult patients with moderately to severely active UC (Mayo score 6 to 12 with endoscopic subscore ≥ 2) was demonstrated in a randomized, double-blind, placebo-controlled trial evaluating efficacy endpoints at Week 6 and Week 52 (C13006). At Week 6, a greater percentage of patients treated with vedolizumab achieved clinical response (47%, $P < 0.0001$) and clinical remission (17%, $P < 0.001$) compared to patients treated with placebo (26% and 5% for clinical response and remission, respectively, Table 4).

Table 4 Study C13006 Efficacy Results at Week 6 (UC Patients)

Endpoint	Placebo (N=149)	Vedolizumab (N=225)
Clinical response rate	26%	47% ($p < 0.0001$)
Clinical remission rate	5%	17% ($p < 0.001$)

Source: Study C13006 CSR, Table 14.3.1.2A (clinical response); Table 14.3.1.4A (clinical remission)

At Week 52, a greater percentage of patients achieved clinical remission in groups treated with 300 mg Q8W (42%, $P < 0.0001$) or Q4W (45%, $P < 0.0001$) vedolizumab as compared to placebo (16%, Table 5). These data support the proposed Q8W dosing frequency because clinical remission rates were similar for Q8W and Q4W dosing regimens at Week 52 and more intensive dosing (Q4W) did not provide additional clinical benefit.

Table 5 Study C13006 Efficacy Results at Week 52 (UC Patients)

Endpoint	Placebo (N=126)	Vedolizumab Q8W (N=122)	Vedolizumab Q4W (N=125)
Clinical remission rate	16%	42% ($p < 0.0001$)	45% ($p < 0.0001$)

Source: Study C13006 CSR, Table 14.3.1.2AM (clinical remission)

Crohn's Disease

The primary efficacy endpoint in the pivotal Phase 3 studies (C13007 and C13011) was based on complete Crohn's Disease Activity Index (CDAI) score which is a widely used

assessment tool of CD disease activity in clinical studies. CDAI score is a composite index of 8 disease activity variables (number of liquid stools, abdominal pain, general wellbeing, extraintestinal complications, use of antidiarrhoeal drugs, abdominal mass, hematocrit, and body weight) ranging from 0 to approximate 600.

The primary efficacy endpoints used in Study C13007 are presented in Table 6.

Table 6 Study C13007 Primary Efficacy Endpoints

	Primary efficacy endpoints
Induction Phase	<ul style="list-style-type: none"> • Clinical remission at Week 6: CDAI \leq 150 points • Enhanced clinical response at Week 6: \geq 100-point decrease in CDAI from baseline (Week 0)
Maintenance Phase	<ul style="list-style-type: none"> • Clinical remission at Week 52: CDAI of \leq 150 points.

For Study C13011, the primary efficacy endpoint is presented in Table 7.

Table 7 Study C13011 Primary Efficacy Endpoints

	Primary efficacy endpoints
Induction Phase	<ul style="list-style-type: none"> • Clinical remission at Week 6: CDAI \leq 150 points

Biomarker: CRP Levels

CRP was used as a biomarker as CRP was considered as a measure of inflammation in patients with CD (i.e., higher CRP was associated with more inflammation and; therefore, more severe disease).

Reviewer's comment: CRP is highly variable, nonspecific and usually considered as an exploratory biomarker. Therefore, CRP is not a validated biomarker for measuring the response to treatment in subjects with CD.

Efficacy results: The efficacy of vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450) was evaluated in a randomized, double-blind, placebo-controlled trial which evaluated efficacy endpoints at Week 6 and Week 52 (C13007). For the two primary endpoints at Week 6 (Table 8), a higher percentage of patients treated with vedolizumab achieved clinical remission (15%, $p < 0.025$) as compared to placebo (7%) at; however, the difference in the percentage of patients who demonstrated enhanced clinical response was not statistically significant (31% and 26% for VDZ and placebo, respectively).

Table 8 Efficacy Results for Study C13007 at Week 6 (CD Patients)

Endpoint	Placebo (N=148)	Vedolizumab (N=220)
Clinical remission rate	7%	15% (p<0.025)
Enhanced clinical response rate	26%	31%

Source: Study C13007 CSR, Table 14.3.1.2A and Table 14.3.1.4A

At Week 52, a greater percentage of patients achieved clinical remission in groups treated with 300 mg Q8W (39%, P<0.001) or Q4W (36%, P<0.01) vedolizumab as compared to placebo (22%, Table 9). These data support the proposed Q8W dosing frequency because clinical remission rates were similar for Q8W and Q4W dosing regimens at Week 52 and more intensive dosing (Q4W) did not provide additional clinical benefit.

Table 9 Efficacy Results for Study C13007 at Week 52 (CD Patients)

Endpoint	Placebo (N=153)	Vedolizumab Q8W (N=154)	Vedolizumab Q4W (N=154)
Clinical remission rate	22%	39% (p<0.001)	36% (p<0.01)

Source: Study C13007 CSR, Table 14.3.1.2AM (clinical remission)

2.2.3 What is the pharmacodynamic (PD) endpoint and what are the PD findings?

MAdCAM-1-Fc (a PD marker) were used to establish the relationship between vedolizumab serum concentration and extent of $\alpha_4\beta_7$ binding saturation by vedolizumab. Act-1 is a mouse monoclonal antibody from which the idiotypic domains of vedolizumab were derived and, therefore, has the same binding site as vedolizumab to target $\alpha_4\beta_7$. MAdCAM-1-Fc is a fusion of MAdCAM-1 with the heavy and light chain Fc of a mouse monoclonal antibody. MAdCAM-1 is the natural ligand for the $\alpha_4\beta_7$ integrin. In these assays, the levels of Act-1 and MAdCAM-1-Fc binding are detected on the surface of cells bearing the $\alpha_4\beta_7$ integrin and are indicative of the number of free $\alpha_4\beta_7$ binding sites (sites not blocked by vedolizumab). Therefore, vedolizumab inhibition of Act-1 and MAdCAM-1-Fc binding to the $\alpha_4\beta_7$ binding site is representative of the extent of $\alpha_4\beta_7$ binding saturation by vedolizumab.

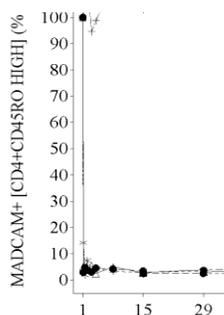
As MAdCAM-1 is the natural ligand for $\alpha_4\beta_7$ integrin and its assay had advantages over the Act-1 assay (including reduced likelihood of interference from neutralizing HAHA), MAdCAM-1-Fc data is considered to be the primary binding biomarker, and these data form the focus of this review.

Maximum $\alpha_4\beta_7$ binding saturation by vedolizumab (i.e., almost 100% inhibition of MAdCAM-1-Fc binding to $\alpha_4\beta_7$) was achieved within 1 hour after the first vedolizumab dose at all dose levels (2-10 mg/kg), shown in Figure 2, in Study 13002. Subjects received a total of 4 vedolizumab doses administrations at Days 1, 14, 29 and 85 and the maximum inhibition remained throughout the whole treatment period until Days 169 (84 days post last dose), 211(126 days post last dose) and 197 (112 days post last dose) for the 2-, 6- and 10-mg/kg dose cohorts, respectively. These data suggested that the higher doses (6- and 10-mg/kg) were associated with prolonged $\alpha_4\beta_7$ binding inhibition and additional time (~30-40 days) was needed for the $\alpha_4\beta_7$ binding sites to recover. Of note the corresponding observed

mean vedolizumab concentrations on the days when loss of near maximal $\alpha_4\beta_7$ inhibition occurred were approximately 2 - 6 $\mu\text{g/mL}$ (Table 10).

Given the proposed dosing regimen (300 mg Q8W, i.e., ~ 4 mg/kg Q8W), near maximum $\alpha_4\beta_7$ binding would be maintained during the entire dosing interval for the majority of subjects receiving the proposed 300 mg Q8W (mean trough ~10 $\mu\text{g/mL}$) dosing regimen.

Figure 2 Mean Percent of Baseline %MAdCAM-1-Fc⁺ Over Time by Vedolizumab Dose (C13002)



1

Source: Study C13002, Figure 14.2.4C.

Abbreviations: MadCAM-1 = mucosal addressin cell adhesion molecule-1.

Vedolizumab administered by 30 minute intravenous (IV) infusion on Days 1, 15, 29, and 85.

Table 10 Mean Vedolizumab Concentrations Over Time By Dose Cohorts

Mean Vedolizumab Concentrations ($\mu\text{g/mL}$, $\pm\text{SD}$)			
	2.0 mg/kg	6.0 mg/kg	10 mg/kg
Day 169	2.0 (± 1.1) (N=9)	10.2 (± 6.0) (N=14)	14.5 (± 11.0) (N=10)
Day 197	0.5 (± 0.4) (N=9)	4.3 (± 3.7) (N=14)	6.2 (± 5.7) (N=11)
Day 211	1.1 (± 3.0) (N=9)	4.3 (± 3.6) (N=9)	3.3 (± 3.3) (N=11)

Source: Study C13002 CSR, Table 14.2.2.2

Bold text indicates vedolizumab concentration data on the day of loss of response for each dose cohort.

2.2.4 Did the applicant conduct studies to evaluate the impact of vedolizumab on system immune response?

Yes. In Study C13012, vedolizumab did not affect CD4^+ and CD8^+ lymphocyte counts or the $\text{CD4}^+:\text{CD8}^+$ ratio in the cerebrospinal fluid (CSF) of healthy subjects (N = 14) at 5 weeks after a single 450-mg infusion of vedolizumab. Additionally, single 300 mg or 600 mg infusions of vedolizumab did not affect on CD34^+ hematopoietic progenitor cells in healthy subjects, but increased other cell populations (consistent with its purported mechanism; i.e., CD4^+ , CD45RO^+ bright, CD25^+ , β_7^+ bright cells and CD8^+ , CD45RO^+ bright, CD25^+ , β_7^+ bright cells). The clinical relevance of these findings is unclear.

2.2.5 Are the active moieties in serum and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moiety, vedolizumab, was measured by a validated enzyme-linked immunosorbent assay (ELISA). In this assay, a mouse anti-vedolizumab idiotypic antibody was immobilized on microtiter plates to capture vedolizumab. Please refer to Section 2.6 Analytical for more information about the performance of this bioanalytical assay.

2.2.6 Exposure-Response

2.2.6.1 What data from the phase 2 studies contributed to the selection of the phase 3 doses?

Ulcerative Colitis

From two dose-ranging Phase 2 studies C13002 and M200-022, there was no apparent dose-response relationship observed. The data for clinical response at day 43 of both studies are summarized in Table 11. However, there are differences with respect to study design (small number of patients), study population (Phase 2 studies have patients with mildly active UC), and endpoint selection which makes the determination of the adequacy of induction dose challenging.

Table 11 Phase 2 Dose-Response for Efficacy Show Similar Response Across Dose Groups within each Study.

Study	*M200-022		*C13002		
	Dose	Dose	Dose	Dose	Dose
	0.5 mg/kg N = 58	2 mg/kg N = 60	2 mg/kg N = 12	6 mg/kg N = 14	10 mg/kg N = 11
**Clinical Response at Day 43	38 (66%)	32 (53%)	6 (50%)	9 (64%)	6 (55%)

* Study M200-022 used drug product from a murine cell line (Process A), whereas study C13002 used drug product from chinese hamster ovary cells (Process B)

** Clinical Response measured by UCCS (M200-022) and Partial Mayo Score (C13002), respectively.

Therefore, exposure-response analysis was conducted using the data from the registration trial C13006 (See Section 2.2.6.2).

Crohn's Disease

Dose-response data were not available for the induction phase as the dose selection rationale from the phase 2 studies did not include a dose-ranging assessment. Instead, the sponsor leveraged on integrin receptor binding data, dose-response in UC patients, and safety data from a 10 mg/kg cohort in trial C13002 to inform the phase 3 dose to be studied in CD patients.

2.2.6.2 What are the characteristics of the exposure-response (E-R) relationship for effectiveness?

In both UC and CD trials, the E-R analysis was based on the ITT population for induction phase as well as for maintenance phase. The ITT population of induction phase has two parallel treatment groups: 300 mg vedolizumab vs. placebo treatment at Week 0 and Week 2; the ITT population of maintenance phase has three parallel treatment groups: placebo, 300 mg Q8W and 300 mg Q4W. The ITT population of maintenance phase consisted of responders from both the ITT population and non-ITT population in induction phase.

In this review, the exposure variable used in the E-R analysis was the trough concentration at Week 6 for induction phase and average through concentration for maintenance phase. The primary response variable used in the E-R analysis was the clinical remission at both Week 6 and Week 52. Additional exploratory response variables were time to treatment failure and time to disease worsening.

Ulcerative Colitis

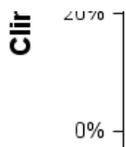
In the pivotal study (C13006) the rate of clinical response at Week 6 (primary efficacy endpoint) for vedolizumab treatment was 47.1 % versus 25.5% in the placebo group, with a difference of 21.7% (95% CI: 11.6, 31.7; $p < 0.0001$). The difference from placebo in remission rate at Week 52 (primary end point) was 26.1% (95% CI: 14.9, 37.2) for Q8W and 29.1% (95% CI: 17.9, 40.4) for the Q4W dosing group. It is important to note that the efficacy of vedolizumab for both induction and maintenance therapy was consistently observed, independent of underlying demographic factors and disease characteristics, such as age, gender, disease location, baseline severity of disease, previous TNF α antagonist use, previous treatment failure, and concomitant medications at baseline.

Induction Exposure-Response

A significant exposure-response relationship for clinical response and remission in the induction phase provides supportive evidence of effectiveness. Furthermore, exposure-response analysis (Figure 3) indicates that higher dose may provide additional benefit in the induction phase. However, considering totality of evidence presented in the application for both induction and maintenance phases, the proposed dose of 300 mg at week 0 and 2 in the induction phase appears reasonable for regulatory approval. We do recommend sponsor to explore (post-approval) the possibility of higher doses in the induction phase with an aim to achieve higher responder rate.

Significant relationships was established between clinical response or remission at week 6 (induction phase) and vedolizumab week 6 trough concentration using logistic regression (Figure 3) demonstrates the exposure response relationship for clinical remission at week 6 depicting that higher exposures may be associated with higher efficacy.

Figure 3 Exposure-Response Relationships for Clinical Response and Remission at Week 6 with Week 6 Vedolizumab Trough Concentrations



However, it is possible that the exposure-response relationships are confounded by several risk factors, such as previous TNF α antagonist use, previous treatment failure, and concomitant medications at baseline. Distributions of these factors are not balanced across the concentrations quartiles at week 6 (Table 12). For example, higher clinical remission in the patients with fourth quartile of exposures may also be driven by the fact that they had less proportion (20% vs. 38-43%) of patients that had failed TNF α antagonist and higher proportion of patients with baseline concomitant immunomodulator use (43% vs. 23-38%).

Table 12 Distribution of Risk Factors by Concentration Quartiles at Week 6 (C13006, Intent-to-Treat Population)

Risk factors	Placebo (N=137)	Mean level in each Concentration Quartile			
		1 (N=53)	2 (N=52)	3 (N=55)	4 (N=54)
VDZ Concentration at Week 6 ($\mu\text{g/mL}$)	0	11	21	28	44

Age	41	44	39	39	39
Gender (Male)	65%	58%	69%	62%	41%
Baseline Mayo score	9	9	8	9	8
Baseline Fecal Calprotectin (mg/kg)	2360	3495	2060	2595	2363
Albumin (g/L)	37	36	38	39	41
Previous Exposure to TNF α antagonist	50%	49%	48%	47%	22%
Prior TNF α antagonist Failure	42%	43%	38%	42%	20%
Baseline Concomitant Immunomodulator Use	31%	28%	23%	38%	43%

Considering the imbalance in risk factors, multivariate logistic regression was also conducted to account for potential confounding factors like baseline mayo score, prior immunomodulator use and prior TNF alpha failure status. Exposures were still significant after adjusting for these factors indicating that higher dose may provide additional benefit.

However, it is worth noting that evidence suggests a delay in achieving response in the induction phase with vedolizumab; therefore, measuring clinical response or remission at Week 6 may be too early. Applicant conducted an analysis showing that among patients who failed to demonstrate response at Week 6, clinical response was observed at Weeks 10 and 14 for greater proportions of vedolizumab patients (25.0% and 27.2%, respectively) compared with placebo patients (14.6% and 20.7%, respectively) (Table 13). These results indicate that patients who did not initially respond to treatment by Week 6 may benefit from an additional 4 to 8 weeks of treatment.

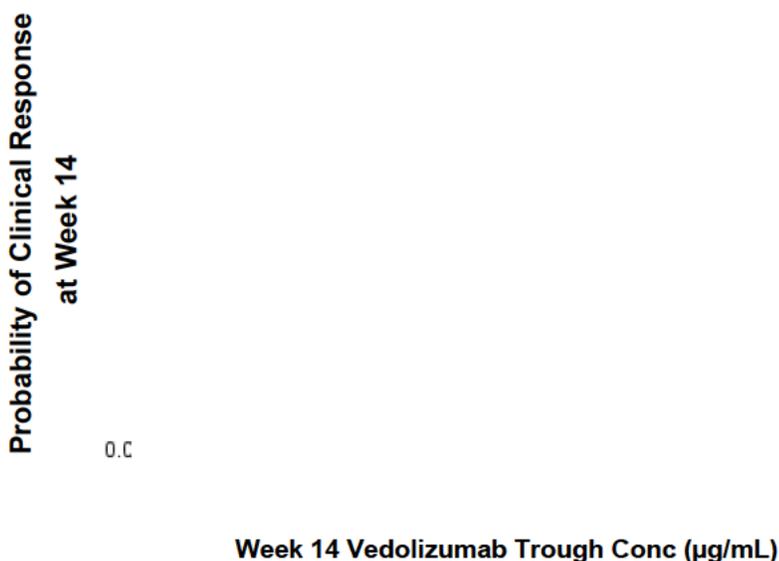
Table 25 Delayed Response Population (Clinical Response by Partial Mayo Score at Week 10 and 14 in Non-Responders at Week 6) in Study C13006

Clinical Response¹
Clinical Response ^b
n (%)
95% CI
Clinical Response ^b
n (%)
95% CI

(Source: [Table 14.3](#) Clinical Study Report for Trial C13006, Table 14.3.1.17M)

Additional analysis was performed by the FDA reviewer to explore relationship between clinical response and trough concentration at Week 14. No exposure-response was evident indicating that exposures achieved by Week 14 may be adequate to achieve clinical response at Week 14 (Figure 4).

Figure 4 No Significant Exposure-Response Relationship for Clinical Response at Week 14 (Study C13006)



In addition, the applicant conducted a trial C130011 in Crohn's disease patients which also provides evidence of delayed response. With an additional Week 6 dose of vedolizumab, the difference in clinical remission over placebo increased from 6.9% to 15.5%, from Week 6 to Week 10. Induction therapy beyond 6 weeks may provide additional benefit because pharmacologic inhibition of lymphocyte migration to the gut may require a longer timeframe for optimal induction efficacy for patients who have failed TNF α antagonists, in particular in more severe patients. Even though Crohn's disease is a different disease but still falls under the umbrella of inflammatory bowel disease. This finding serves as supportive evidence that a delayed response phenomenon may be associated with vedolizumab.

Considering all of the arguments described above, we agree with the sponsor proposed dosing regimen but recommend them to explore option of higher induction doses post-approval.

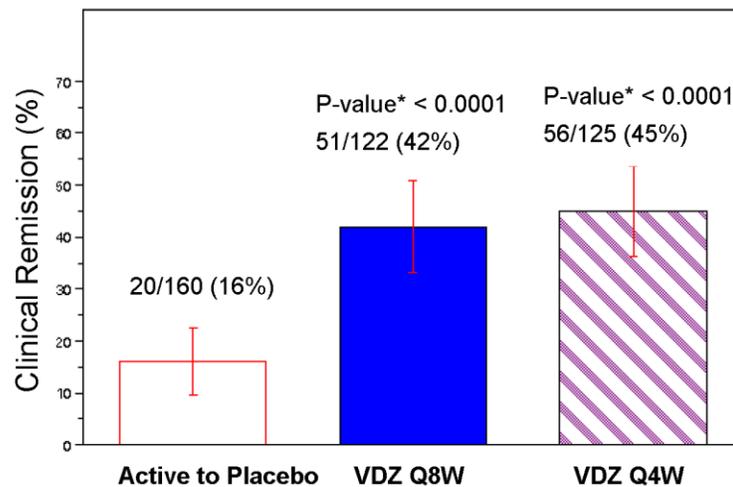
Maintenance Exposure-Response

No dose- or exposure-response relationships were evident for the probability of clinical remission at Week 52 in the pivotal trial C13006.

The efficacy, measured as clinical remission, of both Q8W and Q4W dosing regimen was significantly higher than placebo. However, there appears to be no additional clinical benefit with Q4W compared to Q8W dosing regimen because the proportions of subjects achieved clinical remission at Week 52 were found similar between the Q8W and Q4W vedolizumab regimens (Figure 5). Furthermore, when the data was visualized longitudinally based on clinical remission as indicated by partial Mayo score. It is evident that both Q4W and Q8W dosing regimen provide similar clinical benefit over time (Figure 6).

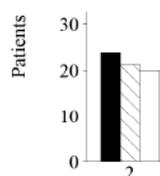
The applicant also evaluated other exploratory endpoints (time to disease worsening and treatment failure). Time to disease worsening was defined as an increase in partial Mayo score of ≥ 3 points from the Week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 6 value > 6) and a partial Mayo score ≥ 5 points. Treatment failure was defined as disease worsening, need for rescue medications or surgical intervention for treatment of UC, or study drug-related AE leading to discontinuation from the study. Based on these endpoints, there appears to be no difference between Q4W and Q8W dosing regimen (Figure 7, Figure 8).

Figure 5 No difference between Q4W and Q8W Clinical Remission (95% CI) by Treatment Group at Week 52 (Study C13006)



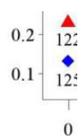
(Source: Sponsor's Clinical Study Report for Trial c13006, Figure 14.3.1.2DM)

Figure 6 No Dose Response is evident in the temporal profiles of clinical remission, based on partial Mayo score, between the Q4W and Q8W dosing regimens in trial C13006



- PLA (Active-to-placebo group): responders at Week 6 and re-randomized to placebo group in the maintenance phase (Source: Sponsor's Clinical Study Report for Trial C13006, Figure 14.3.1.25BM)

Figure 7 No Dose Response is Evident between the Q4W and Q8W dosing regimens in the Kaplan Meier Survival Curves of Time to Treatment Failure (Study C13006)



(Source: Sponsor's Clinical Study Report for Trial C13006, Figure 14.3.1.19BM)

Figure 8 No Dose Response is Evident between the Q4W and Q8W dosing regimens in the Kaplan Meier Survival Curve of Time to Disease Worsening (Study C13006)

(Source: Sponsor's Clinical Study Report for Trial C13006, Figure 14.3.1.19AM)

Based on these findings, the proposed maintenance dose and dosing interval (300 mg every 8 weeks) is acceptable.

For details on the applicant's exposure-response analysis please see Section 3.1 of the Pharmacometric Review.

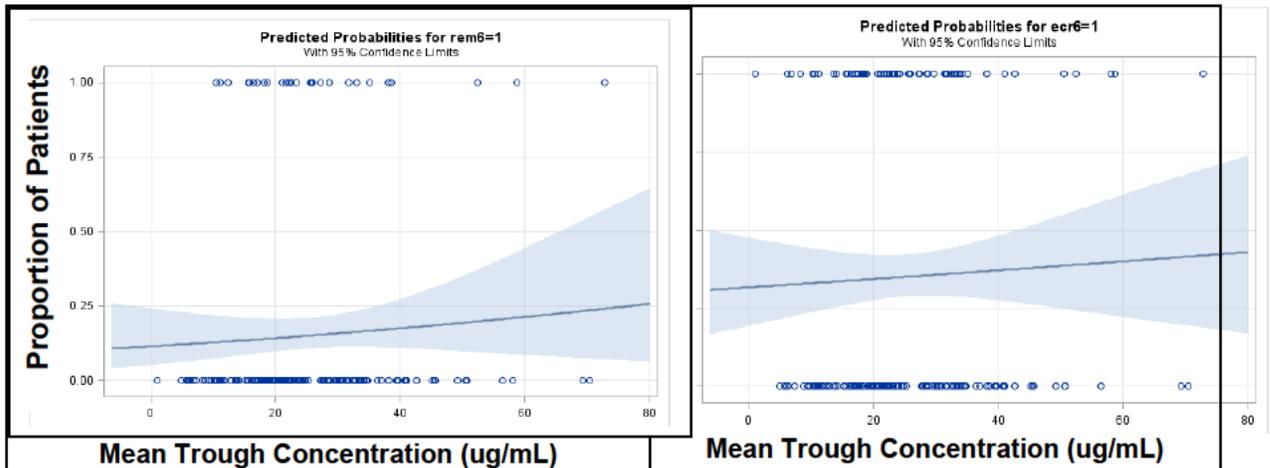
Crohn's Disease

Induction of Clinical Remission and/or Enhanced Clinical Response

Exposure-response was not evident for the induction of clinical remission or enhanced clinical response at Week 6 (primary efficacy end points), based on mean trough concentrations at Week 6. Exposure-response analyses consisted of both univariate and multivariate logistic regressions to account for potential confounding factors. In no case was the mean trough concentration a significant predictor of clinical remission or enhanced clinical response. Further details on the multivariate logistic regression results are shown in the Pharmacometric Review. Results of the univariate analysis testing clinical remission and enhanced clinical response as a function of mean trough concentration are shown in Figure 9. Although a minor slope is observed in the plots, the p-value is 0.6 and in no multivariate analysis was exposure considered a significant predictor of remission or enhanced clinical response.

Based on these analyses, the proposed dose regimen of 300 mg administered at Weeks 0 and 2 appears reasonable.

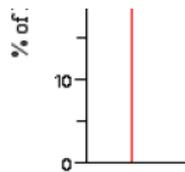
Figure 9 No Significant E-R Relationship for the Probability of Clinical Remission (left panel) or Enhanced Clinical Response (right panel) at Week 6 (Study C13007)



Maintenance of Clinical Remission and/or Enhanced Clinical Response

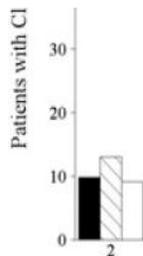
There is no dose-response for efficacy observed between the Q8W and Q4W dosing intervals either at Week 52 (Figure 10) or over time (Figure 11). Average values of the mean trough concentrations throughout the maintenance phase from each individual were 36% higher for the Q8W dosing group compared to the Q4W dosing group. Additionally, exposure-response analyses, including both univariate and multivariate logistic regressions, do not indicate a relationship between mean trough concentration and the probability of achieving clinical remission or enhanced clinical response at week 52 (Figure 12). Thus, the proposed maintenance dose of 300 mg every 8 weeks is acceptable.

Figure 10 No Dose-Response Observed in Clinical Remission at Week 52 for Q4W or Q8W Cohorts (Study C13007)



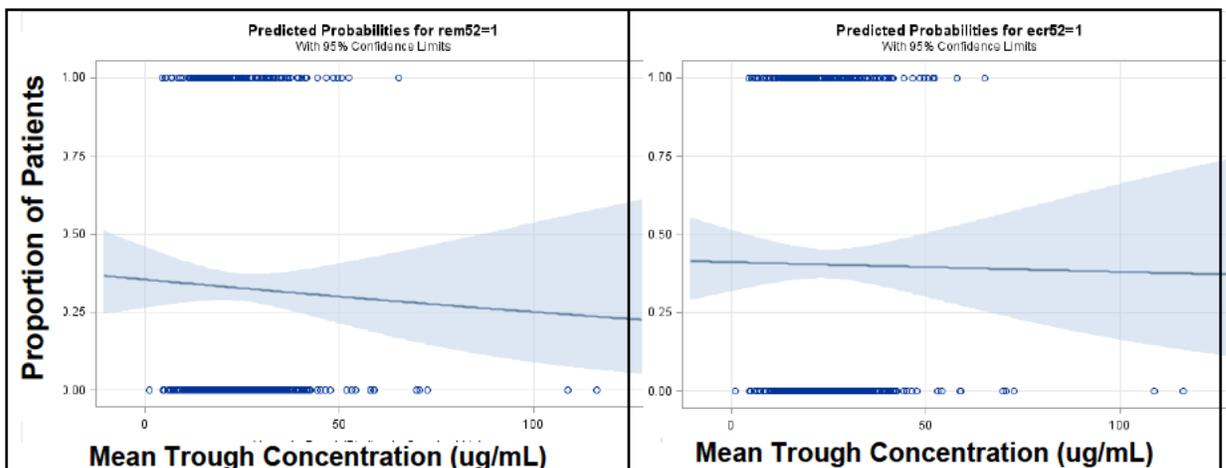
(Source: Sponsor's Clinical Study Report for Trial C13007, Figure 10)

Figure 11 No Evident Dose Response in the Temporal Profiles of Clinical Remission Between Q8W and Q4W Dosing Cohorts (Study C13007)



(Source: Sponsor's Clinical Study Report for Trial c13007, Figure 25)

Figure 12 No Significant E-R Relationship for the Probability of Clinical Remission (left panel) or Enhanced Clinical Response (right panel) at Week 52 (Study C13007)



For details on the sponsor's analysis, please see the Pharmacometric Review.

2.2.6.3 What are the characteristics of the exposure-response relationship for safety?

Model-based exposure-safety analyses were not performed. There was no obvious dose regimen-dependent pattern in overall adverse events (AEs), serious adverse events (SAEs), discontinuation due to AE, or death.

2.2.6.4 Does this drug prolong QT/QTc Interval?

No. The potential for vedolizumab to affect the QT interval was assessed in Study C13009. Study C13009 Part 2 was a randomized, placebo-controlled, double-blind, parallel-group study in which subjects were randomized in a 1:1:1 ratio to receive single IV doses of 600-mg Process B vedolizumab, 600-mg Process C vedolizumab, or placebo. The study was conducted in healthy male or female subjects, aged 18 to 45 years (N=73).

The largest time-matched mean baseline adjusted difference between vedolizumab and placebo was observed on Day 8, when the adjusted mean change from baseline was -4.5 msec for placebo and 0.6 msec for vedolizumab. The 1-sided 95% (or 2-sided 90%) upper confidence bound for the largest mean change adjusted for placebo was 9.3 msec after 600 mg vedolizumab administration, observed on Day 8. This upper bound was below 10 msec, which is the threshold for pharmacologic effect on cardiac repolarization as detected by QT/QTc prolongation. Therefore, no effect of vedolizumab on QTc was observed. Please refer to interdisciplinary QT review for more details.

2.2.6.5 Is there evidence to support increase dosing frequency from Q8W to Q4W if lack or decrease of response?

UC Patients

No. The applicant has not demonstrated that dose escalation from Q8W to Q4W will result in greater efficacy.

The applicant is proposing that some patients who did not benefit from the Q8W regimen derived benefit from more frequent dosing with the Q4W regimen. The evidence was that 32 patients who discontinued from vedolizumab Q8W dosing, predominantly due to lack of efficacy, and transitioned to Q4W dosing in Study C13008 showed a clinical remission rate of 6% (2/32) at Week 0 that increased to 25% (8/32 patients) at Weeks 28 and 52. The argument against this is based on the fact that this was not a controlled assessment. That is, there was no comparison to subsequent treatment with Q8 weeks. Therefore, it is not possible to discern whether the additional benefit was due to additional time on treatment or the higher dose. Furthermore, based on the randomized comparison of two doses in the maintenance phase, there appears to be no additional benefit for the higher dose. Therefore considering totality of evidence, there is not enough rationale for dose escalation from Q8W to Q4W in case of lack or decrease of response.

CD Patients

No. The applicant has proposed increasing the dose in patients who exhibit a decrease in response or lack of response. However, their data was not studied in such a way that this claim can be supported. The applicant is claiming that data from patients that were considered treatment failures due to lack of efficacy in the Q8 weekly dose group and subsequently enrolled in study C13008 (n=57) to receive vedolizumab Q4 weekly provided evidence of additional benefit -- 32% (n=18) of these patients achieved remission by Week 52. The argument against this is based on the fact that this was not a controlled assessment. That is, there was no comparison to subsequent treatment with Q8 weeks. Therefore, it is not possible to discern whether the additional benefit was due to additional time on treatment or the higher dose.

2.2.6.6 Is the response observed at Week 14 predictive of that at Week 52? (“Reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14”?)

UC Patients

Yes. The applicant’s labeling statement to “reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14” in the proposed label appears reasonable.

The analysis was conducted for two groups of patients. The first group is vedolizumab treated patients that did not obtain response up to Week 14. The second group is vedolizumab treated patients that responded initially at Week 6 but lost response at Week 14. Of the 198 patients in the first group, only 10 (4%) remitted by Week 52. Of the 53 patients in the second group, only 2/28 (7%) and 2/25 (8%) remitted by Week 52 in Q8W

and Q4W; lower than the remission rate of 19.5% in the placebo group of Study C13006. The low remission rates support sponsor’s statement by suggesting that for non-responders at Week 14, it is unlikely that they would regain any additional benefit afterwards, regardless of their response status before Week 14.

CD Patients

Yes, the applicant’s statement in the proposed label to “reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14” is reasonable. Of the patients that did not obtain remission at Week 14 (n = 98 for Q8W and n=91 for Q4W), 18% (n=18) remitted by Week 52 for the Q8W dose group and 22% (n=20) remitted by Week 52 for the Q4W dose group; similar to the remission rate of 21.6% in the placebo group of Study C13007.

Please refer to the Pharmacometric Review for further details.

2.2.7 What are the PK characteristics of the drug?

As noted in section 2.1.1, vedolizumab PK characteristics were well characterized in studies with Process B or C drug products. Additional PK data from studies with Process A (comparability to Process B or C is unknown) would not add value to the overall assessment of vedolizumab. Therefore, only PK data from Process B or C drug products were presented in the following sections.

2.2.7.1 What are the single and multiple dose PK parameters of vedolizumab in healthy adults?

Vedolizumab PK in healthy subjects was characterized following single-dose administration but not after multiple dose administration.

Table 14 summarized the pharmacokinetics parameters of vedolizumab after single-dose IV infusion administration of fixed doses of 300 and 600 mg (Study C13009) to healthy subjects. The mean clearance (CL) was approximately 0.15 L/day, and mean half-life (t_{1/2}) was 18 to 21 days. Data showed that vedolizumab exposure increased approximately in a dose proportional manner from 300 to 600 mg.

Table 14 Summary of Single-Dose Pharmacokinetic Parameters (300- and 600-mg Vedolizumab)

Dose Parameter	C _{max} (µg/mL)	t _{1/2} (day)	AUC _(0-last) (day*µg/mL)	AUC _(0-inf) (day*µg/mL)	CL (L/day)	V _{ss} (L)
300 mg						
N	10	8	8	8	8	8
Mean (SD)	120 (37.3)	18.3 (4.05)	2000 (271)	2020 (266)	0.151 (0.018)	4.53 (0.646)
CV (%)	31.1	22.1	13.5	13.2	12.2	14.3
Median	107	18.4	1940	1960	0.154	4.46
Min, Max	81.1, 204	13.3, 23.8	1720, 2540	1760, 2550	0.117, 0.170	3.71, 5.64

600 mg						
N	24	22	22	22	22	22
Mean (SD)	211 (50.0)	21.0 (4.39)	3840 (880)	3970 (823)	0.157 (0.031)	5.04 (1.06)
CV (%)	23.7	20.9	22.9	20.7	19.7	20.9
Median	206	19.7	3650	3940	0.153	4.85
Min, Max	128, 383	14.9, 27.5	2200, 6050	2630, 6060	0.099, 0.229	3.60, 8.11

Source: Study C13009 CSR, Table 14.2.1.1

2.2.7.2 What are the PK characteristics of the drug in patients with UC and CD? How does the PK of the drug in healthy adults compare to that in patients?

PK characteristics in subjects with UC and CD:

Sparse trough samples were collected from phase 3 studies and population PK approach was used to estimate the PK parameters based on 5 clinical studies (13002, 13006, 13007, 13009 and 13011). The concentration-time data were best described by a 2-compartment model with zero-order input and parallel linear and nonlinear elimination (See 2.2.7.8 for further details on the nonlinearity in vedolizumab PK). The typical estimates (95% CI) of the pharmacokinetics parameters were presented in Table 15. Population estimates of CL_L (linear clearance) were 0.159 L/day in UC patients and 0.155 L/day in CD patients, and volume of distribution was 4.85 L ($V_c = 3.19$ L and $V_p = 1.66$ L) in both patient populations. Based on the estimated CL_L , vedolizumab $t_{1/2}$ is calculated to be approximately 25 days at the proposed dosing regimen for both indications.

Table 15 Parameter Estimates From Final Population Pharmacokinetic Model

Parameter	Estimate	Bayesian 95% CI
UC CL_L	0.159 L/day	0.152, 0.166
CD CL_L	0.155 L/day	0.149, 0.161
V_c	3.19 L	3.14, 3.25
V_p	1.66 L	1.6, 1.72
V_{max}	0.274 mg/day	0.226, 0.329
Q	0.119 L/day	0.112, 0.127
K_m	0.974 $\mu\text{g/mL}$	0.715, 1.3
$t_{1/2}$	25 days (calculated based on CL_L)	

Source: Population PK and PD Report 2012, Table 9

Abbreviations: CL_L = clearance of linear elimination pathway; CV = coefficient of variation
 K_m = concentration at half-maximum elimination rate; Q = intercompartmental clearance; V_c = central compartment volume; V_{max} = maximum elimination rate; V_p = peripheral compartment volume

Consistent with similar PK parameters in subjects with UC or CD, similar vedolizumab trough concentrations were observed in UC and CD patients administered 300 mg vedolizumab on Weeks 0 and 2, followed by 300 mg vedolizumab every four or eight weeks starting from Week 6 (Table 16).

Table 16 Mean (\pm SD) Vedolizumab Concentrations in ITT Patients with UC and CD from Studies C13006 and C13007

Patient Type	Induction Phase	Maintenance Phase	
	Trough Serum Concentration at Week 6 (μ g/mL)	Trough Serum Concentration at Week 46 (μ g/mL)	
		Q4W	Q8W
Ulcerative Colitis	26.3 (\pm 12.87) (N=210)	42.8 (\pm 28.03) (N=82)	11.2 (\pm 7.24) (N=77)
Crohn's Disease	27.4 (\pm 19.17) (N=198)	32.5 (\pm 18.42) (N=84)	13.0 (\pm 9.08) (N=72)

Source: Study C13006 CSR Table 14.2.1.1BM; Study C13007 CSR Table 14.2.1.1AM

Patients with positive ADA were excluded from this analysis

Comparison between Healthysubjects and subjects with UC or CD:

The estimated PK parameters (CL_L , V_{ss} and $t_{1/2}$) of patients with CD or UC based on population PK analysis (Table 15) were similar to that of healthy subjects based on noncompartmental analysis (0.15 L/day, 4.53 to 5.04 L and 18 to 21 days for mean CL , V_{ss} and $t_{1/2}$ at 300-600 mg dose in healthy subjects, respectively; Table 14).

2.2.7.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

The overall intersubject variability for healthy subjects and patients is generally moderate (Table 17). The intrasubject variability was not assessed.

Table 17 Summary of Vedolizumab Intersubject Variability in Pharmacokinetic Parameters

Population	Intersubject Variability (%CV)				
	AUC	C_{max}	$t_{1/2}$	CL	V_{ss}
Healthy Subjects ^a	13.5 – 22.9 ^c	23.7 - 31.1	20.9 - 22.1	12.2 - 19.7	14.3 - 20.9
Subjects with UC and CD (population PK) ^b	NA	NA	NA	36.6	19.1 ^d

a: Table 9; b: Table 10; c: AUC_{0-inf} ; d: V_e .

2.2.7.4 What are the characteristics of drug absorption?

Not applicable as vedolizumab will be administered intravenously.

2.2.7.5 What are the characteristics of drug distribution?

Vedolizumab volume of distribution (V_{ss}) after single-dose administration in healthy subjects in Study C13009 was 4.49 L (14.3% CV) at 300-mg vedolizumab (Table 14). In patients, vedolizumab V_{ss} was estimated to be 4.85 L ($V_c = 3.19$ L and $V_p = 1.66$ L) based on population PK analysis (Table 15).

In Study 13012, vedolizumab concentrations in CSF was measured in samples obtained prior to and after the 30-minute IV infusion of vedolizumab 450 mg at 5 weeks. None of these samples had detectable vedolizumab (detection limit of vedolizumab in this assay was 0.125 $\mu\text{g/mL}$) in the CSF. The mean serum vedolizumab concentration at Week 5 was 34.47 $\mu\text{g/mL}$ (Study C13012 CSR Table 14.2.1.2A), indicating that no measurable vedolizumab was distributed into the CSF when the serum vedolizumab concentration dropped ~ 34.47 $\mu\text{g/mL}$. Given that mean steady state vedolizumab peak concentrations were above this level (~ 100 $\mu\text{g/mL}$) in 300 mg Q8W dose cohort (Study C13006 CSR Table 14.2.1.1BM), the clinical relevance of this data is unknown. It is uncertain whether vedolizumab would distribute into CSF throughout the whole drug treatment period.

2.2.7.6 What are the characteristics of drug metabolism?

As a monoclonal antibody, vedolizumab is expected to be degraded into small peptides and amino acids.

2.2.7.7 What are the characteristics of drug elimination in urine?

As a monoclonal antibody with a MW of 146 KDa, vedolizumab is not expected to be eliminated in urine.

2.2.7.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Vedolizumab exhibited nonlinear PK when the dose is under or equal to 2 mg/kg and linear PK over the dose range 6 to 10 mg/kg based on single dose PK data from healthy subjects (Figure 13 and Figure 14). After multiple dosing, dose-proportional PK was observed over dose range 2-10 mg/kg in UC patients (Figure 15).

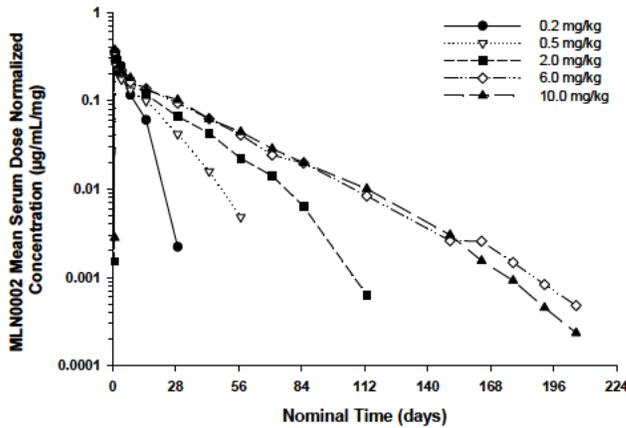
Single-dose pharmacokinetics data following IV administration in healthy subjects are available over a dose range of 0.2 to 10 mg/kg vedolizumab using vedolizumab Process B (Study C13001). Maximum vedolizumab serum concentrations were achieved at or near the end of infusion and declined in a bi-exponential manner until the concentrations reached approximately 1 to 10 $\mu\text{g/mL}$ where nonlinearity is observed (Figure 13, Figure 14). This is consistent with the target mediated disposition where the nonlinear clearance pathway is saturated at high concentrations.

Figure 13 Mean Concentration-time Profile in Healthy Subjects Following Single-Dose Administration (log-linear plot) as IV infusion over 30 minutes (C13001)



Source: Study C13001 CSR, Listing 16.2.6.1.

Figure 14 Dose-Normalized Mean Concentration by Nominal Actual Dose in Healthy Subjects Following Single-Dose Administration (log-linear plot) (C13001)



Source: Study C13001 CSR, Listing 16.2.6.1.

Dose: 30-minute intravenous infusion of 0.2-10 mg/kg vedolizumab.

BLQ values were set to zero.

Similar to the findings from healthy subjects, vedolizumab pharmacokinetics demonstrated dose proportionality over the dose range of 2 to 10 mg/kg in UC patients. In Study C13002 (in UC patients), following a 30-minute IV infusion of vedolizumab (Process B) on Days 1, 15, 29, and 85, serum concentrations increased in an approximately dose-proportional manner (Figure 15).

Figure 15 Semilogarithmic Plot of Mean Vedolizumab Serum Concentrations Over Time by Dose Cohort

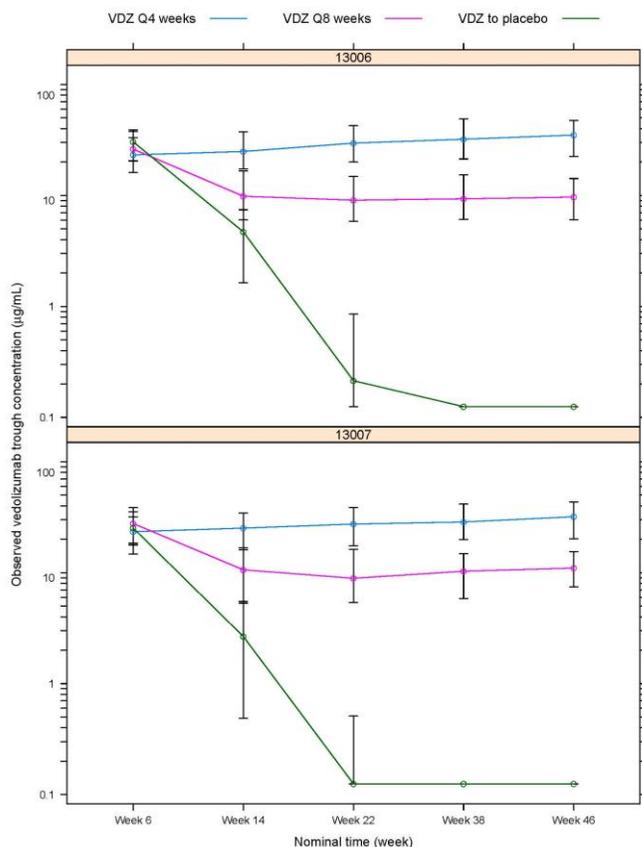
Source: Study C13002 CSR, Figure 14.2.2B

2.2.7.9 How do the PK parameters change with time following chronic dosing?

The estimated typical vedolizumab half-life at the 300-mg dose is approximately 25 days based on population PK approach. For Q8W dose regimen, the accumulation index is predicted to be minimal (1.2- to 1.3-fold).

In phase 3 studies, the administration of a loading dose of vedolizumab (Week 0 and Week 2) precludes the determination of accumulation index. As shown in Figure 16, trough serum concentration was maintained at similar levels after Weeks 6 and 14 for Q4W and Q8W dose regimen, respectively.

Figure 16 Median (Interquartile Range) of Observed Serum Trough Concentration-Time Profile of Vedolizumab (Top Panel -C13006, UC subjects; Bottom Panel - C13007, CD subjects)



Abbreviations: Q4 weeks = every 4 weeks; Q8 weeks = every eight weeks; VDZ = vedolizumab.
Source: Population PK and PD Report 2012, Figure 6 and Figure 7.

2.3 Intrinsic Factors

The effects of the intrinsic factors: age, albumin, fecalprotectin levels, C-reactive protein, CDAI scores, partial Mayo scores, or TNF-naïve status on the pharmacokinetics, specifically the linear clearance CL_L , of vedolizumab were evaluated in the population pharmacokinetics analysis. The effects of body weight were incorporated into the model using allometric relationships based on prior vedolizumab PK analyses. The remaining factors were implemented as exponential factor on CL_L . It is noted that the clinical studies of vedolizumab did not enroll pediatric subjects; therefore, the age impact assessment is limited to adult subjects. Gender was not tested as a covariate in the population model due to correlation with weight, but an exploratory analysis was performed in the individual estimates of pharmacokinetics parameters.

None of the tested covariates on CL_L were considered to be of clinical relevance because the effect sizes were less than $\pm 25\%$ from the typical reference population value when evaluated across a representative range of covariate values and categories in the dataset.

No dose adjustment is necessary for any of the intrinsic factors evaluated.

2.3.1 What are the major intrinsic factors for the inter-subjects variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease?

2.3.1.1 Severity of Disease State

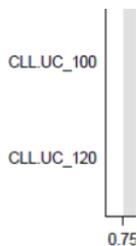
The following baseline covariates were tested in the population PK model as a measure of severity of disease state: Partial Mayo Score, CDAI Score, fecal calprotectin, and C-reactive protein (CRP). None of the evaluated disease state covariates were identified to have clinically meaningful effect on CL_L. Please refer to PM review for more details.

2.3.1.2 Body Weight

The effect of body weight on vedolizumab PK was assessed in two clinical studies in healthy subjects: Study C13005 and Study 13009; body weight based dosing was used in Study C13005 and fixed dose was used in Study 13009. Additionally, body weight was evaluated as a covariate of CL_L in the population PK analysis based on data from 5 clinical studies (13002, 13006, 13007, 13009 and 13011).

Results from the population PK analysis showed that the effect of body weight on CL_L was statistically significant (Figure 17). The point estimate (95% CI) for body weight impact on CL_L point estimate was 0.368 (0.306, 0.433), i.e., 19% lower CL for body weight of 40 kg versus a 22% higher CL for a body weight of 120 kg when compared to the CL value for 70 kg body weight.

Figure 17. Effect of Body Weight on CL. Distributions are shown for body weight values of 70 kg (median weight), 40 kg, 60 kg, 80 kg, 100 kg, and 120 kg.



(Source: Applicant's Summary of Clinical Pharmacology, Figure 3-12)

Study C13005 was conducted to assess the impact of weight on the pharmacokinetics of vedolizumab in healthy subjects. Healthy subjects with body weights ranging from 46.0 to 129.7 kg received a single dose of 6 mg/kg vedolizumab IV. As shown in Table 18, mean vedolizumab exposures were higher in subjects with high body weight (90 to 130 kg for females and 100 to 140 kg for males) compared to subjects with low body weight (≤ 70 kg for males and ≤ 60 kg for females), suggesting that weight-adjusted dosing overcompensated for exposure of vedolizumab in subjects with higher weight. Therefore, body weight-adjusted dosing may not confer an advantage over fixed doses. As such, phase 3 studies were conducted with fixed dose regimens.

Table 18 Summary of Vedolizumab Pharmacokinetic Parameters [Geometric mean (%CV)] by Body Weight Following A Single Dose (6 mg/kg) Intravenous Infusion C13005

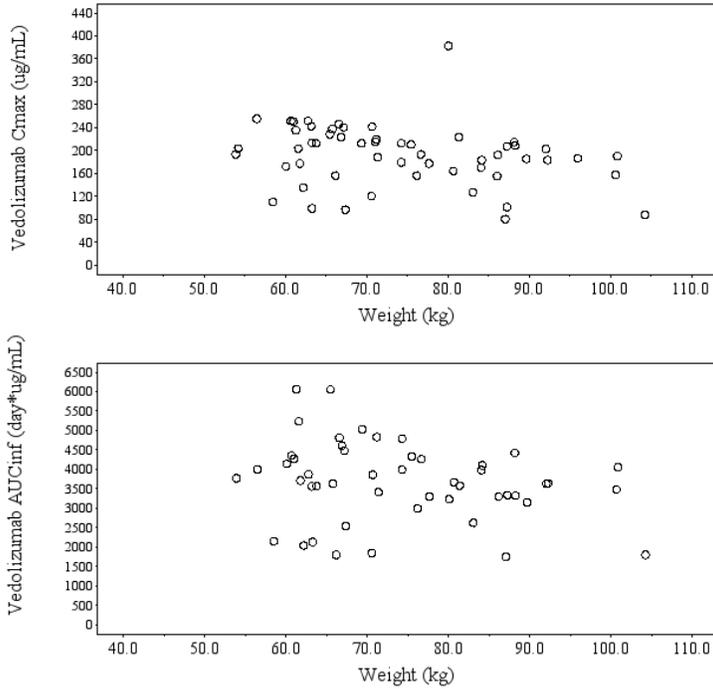
<u>Parameter</u>
C_{max} ($\mu\text{g}/\text{mL}$)
$AUC_{0-t_{last}}$ ($\mu\text{g}\cdot\text{h}/\text{mL}$)
AUC_{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)
V_z (L)
CL (L/day)
$t_{1/2}$ (day)

Source: Study C13005 CSR, Table 14.2.2.1.

In Study C13009, subjects received a fixed dose administration (600 mg). Vedolizumab PK data showed a slight trend of decrease in C_{max} and AUC_{inf} of with increasing body weight (51.8 to 104.7 kg, Figure 18), consistent with the finding from Study C13005.

Overall, the impact of body weight on vedolizumab PK was not considered clinically relevant over range 46.0 to 129.7 kg.

Figure 18 Vedolizumab C_{max} (Top Panel) and AUC_{inf} (Bottom Panel) Versus Weight (C13009) Following Administration of 600 mg



Source: Study C13009, Figure 14.2.3.8A and Study C13009, Figure 14.2.3.8B.

2.3.1.3 Gender

As exploratory analysis, the pharmacokinetics parameters from Study C13009 were summarized by gender (Table 19). Females had slightly higher exposures than males. Mean C_{max} and AUC were 25% and 10% higher in females than in males, respectively. However, this finding is confounded with body weight as females tend to have lower body weight. Therefore, the impact of gender on vedolizumab PK maybe limited.

Table 19 Summary of Vedolizumab Pharmacokinetic Parameters [Geometric Mean (%CV)] Split by Gender (C13009) Following 600 mg Dose Administration

Parameter	Vedolizumab (600 mg)	
	Male	Female
N	31	24
C _{max} (µg/mL) ^a	168 (32%)	210 (23%)
N	27	22
AUC _{inf} (µg*day/mL) ^a	3388 (31%)	3739 (31%)

Source: Study C13009 CSR, Table 14.2.5.1A and Study C13009, Table 14.2.5.1B.

2.3.1.4 Serum Albumin

In the population analysis, albumin is a statistically significant covariate of CL_L of vedolizumab with a point estimate (95% CI) of -1.18 (-1.24, -1.13). The impact of albumin concentration on the clearance of vedolizumab appeared to be moderate. The median serum albumin concentration of subjects in this analysis was 3.7 g/dL with a range of 2.7 to 4.9 g/dL. The change in CL due to albumin ranged approximately from -20% to +30% of the median CL estimate when albumin decreased from the 98.5th percentile (4.7 g/dL) to the 18th percentile (3.2 g/dL), respectively, in this patient population. As the model-predicted CL change is close to $\pm 25\%$, thus dose adjustment based on serum albumin is not necessary.

2.3.1.5 Prior Treatment With TNF α Antagonist Therapy

The effect of prior treatment with TNF α antagonist therapy on vedolizumab CL_L was statistically significant as reflected by the point estimate (95% CI) of its impact on CL_L of 1.04 (1.01, 1.07), i.e., 4% higher CL in subjects with prior anti-TNF α treatment. Given the small extent, the impact of the prior TNF α treatment on CL_L was not clinically meaningful.

2.3.1.6 Elderly (Age)

No dedicated study was conducted to assess the impact of age in the pharmacokinetics of vedolizumab. Population pharmacokinetics modeling showed that age had no impact in the vedolizumab CL_L based on the studies with subjects who are 18-78 years of age.

2.3.1.7 Race

No dedicated study was conducted to assess the impact of race on the pharmacokinetics of vedolizumab.

2.3.1.8 Pediatric Patients

No clinical studies with vedolizumab have been conducted in the pediatric population. A waiver for children (b) (4) and deferral for children age (b) (4) 17 years is submitted in this original BLA. Evaluation in children (b) (4) to 17 years is deferred until an evaluation of safety and benefit-risk profile in adults is completed.

2.3.2 Does genetic variation impact exposure and/or response?

As part of study C13002, DNA was collected from 46 subjects with ulcerative colitis. Genotyping was performed for single nucleotide polymorphisms (SNPs) in the genes *NOD1*, *NOD2*, *MAdCAM1*, *ITGB7*, *SCL22A4*, *CARD8*, *IL23R* and the *IBD5* locus. Subject-level genotype data was submitted for 44 subjects, of which 35 received vedolizumab (2.0-10.0 mg/kg). Analyses performed by the pharmacogenomics reviewer showed no association between genotype and clinical response (defined as a decrease from baseline in the partial Mayo score ≥ 2 points and $\geq 25\%$, as well as a decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1) in this study.

2.3.3 Immunogenicity

2.3.3.1 What is the incidence (rate) of the formation of the anti-drug antibodies (ADA), including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

The combined immunogenicity data from two pivotal phase 3 studies, C13006 (UC) and C13007 (CD), are summarized here.

The definitions of the ADA status in each immunogenicity sample are shown below:

- **Negative ADA sample:** a sample that was negative in the ADA confirmatory assay.
Positive ADA sample: a sample that was positive in both the ADA screening and confirmatory assays.
- **Positive neutralizing ADA sample:** a sample that was positive in the neutralizing ADA assay.

Patient ADA status was grouped into 3 categories as follows:

- **ADA negative subject:** a patient who did not have confirmed positive ADA results in any post baseline sample.
- **ADA positive subject:** a patient who had at least 1 positive ADA result in any post baseline sample.
 - Transiently positive: defined as patients with confirmed positive ADA in only 1 sample at a postdose visit.
 - Persistently positive: defined as patients with confirmed positive ADA in 2 or more positive ADA samples at postdose visits.

The treatment groups were defined as below:

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 Q8W (VDZ/VDZ Q8W): Referring to subjects who responded to treatment with 2 doses of VDZ during induction and were randomized to VDZ Q8W during maintenance for up to 52 weeks.
4. Vedolizumab/vedolizumab Q4W (VDZ/VDZ Q4W): Referring to subjects who responded to treatment with 2 doses of VDZ during induction and were randomized to VDZ Q4W during maintenance for up to 52 weeks.
5. Vedolizumab/vedolizumab Q4W [VDZ/VDZ Q4W (O)]: Referring to subjects who did not respond to treatment with 2 doses of VDZ during induction and were assigned to receive open label VDZ Q4W during maintenance for up to 52 weeks.
6. Vedolizumab/vedolizumab (VDZ/VDZ; combined VDZ population): Referring to subjects who were in the aforementioned VDZ/VDZ Q8W, VDZ/VDZ Q4W, and VDZ/VDZ Q4W (O).

The ADA formation during treatment is presented in Table 20 and Table 21.

Table 20 Summary of Anti-Drug Antibody Status – Safety Population (C13006 and C13007)

ADA Status	Maintenance Study ITT (ie, Responders to vedolizumab induction, randomized to Maintenance Treatment at Week 6)			Non-ITT		Combined
	VDZ/PBO N = 279	VDZ /VDZ Q8W N = 276	VDZ /VDZ Q4W N = 279	PBO/PBO (from Week 0) N = 297	VDZ/VDZ Q4W (O) (Week 6 Nonresponders) N = 879	VDZ/VDZ N = 1434
	ADA-negative, n(%)	234 (84)	268 (97)	276 (99)	288 (97)	834 (95)
ADA-positive, n(%)	45 (16)	8 (3)	3 (1)	8 (3)	45 (5)	56 (4)
Transiently positive	14 (5)	6 (2)	3 (1)	3 (1)	38 (4)	47 (3)
Persistently positive	31 (11)	2 (<1)	0	5 (2)	6 (<1)	8 (1)
Any neutralizing ADA-positive	24 (9)	4 (1)	3 (1)	4 (1)	26 (3)	33 (2)

Source: Integrated Summary of Safety, Table 18.2.7.1A.

One subject in VDZ/VDZ Q4W(O) non-ITT cohort was mis-specified as a persistent ADA positive and therefore the numbers were updated for persistent positive category.

Table 21 Summary of Human Antihuman Antibody Frequency by Study Visit (C13006 and C13007)

	ITT			Non-ITT		Combined
	VDZ/PBO N = 279	VDZ /VDZ Q8W N = 276	VDZ /VDZ Q4W N = 279	PBO/PBO N = 297	VDZ /VDZ Q4W (O) N = 879	VDZ/VDZ N = 1434
Any ADA-positive (%)	45/279 (16)	8/276 (3)	3/279 (1)	8/296 (3)	45/879 (5)	56/1434 (4)
Week 0 Predose	6/277 (2)	2/275 (<1)	1/279 (<1)	3/295 (1)	10/874 (1)	13/1428 (<1)
Week 6	3/277 (1)	2/274 (<1)	2/275 (<1)	6/269 (2)	9/735 (1)	13/1284 (1)
Week 14	9/238 (4)	1/245 (<1)	0/249	3/187 (2)	1/568 (<1)	2/1062 (<1)
Week 26	22/172 (13)	2/176 (1)	0/202	1/105 (1)	0/398	2/776 (<1)
Week 38	17/138 (12)	1/160 (<1)	0/178	1/83 (1)	0/323	1/661
Week 52	20/117 (17)	0/148	0/162	1/74 (1)	0/303	0/613
Final Safety Visit (Week 66)	2/24 (8)	4/26 (15)	1/35 (3)	0/47	27/259 (10)	32/320 (10)
Early Termination	17/155 (11)	1/113 (<1)	0/109	2/205 (1)	8/489 (2)	9/711 (1)

Source: Integrated Summary of Safety Table 18.2.7.1C.
Final Safety Visit which includes Week 66 data.

The immunogenicity of vedolizumab during treatment could not be reliably assessed due to drug interference issue in the immunogenicity assay. Specifically, the mean vedolizumab steady state trough concentrations for 300 mg Q8W and Q4W regimen, respectively, were approximately 10 and 30 µg/mL, respectively (Table 16). These levels were significantly greater than the drug tolerance level (i.e., 500 ng/mL) of immunogenicity assay (refer to section 2.6). Therefore, the incidence rate determined during treatment phase is expected to be under-estimated.

In the combined VDZ/VDZ group, 56 of 1434 (4%) patients developed ADA at any time during treatment. Eight of 56 patients were persistently positive (antibody-positive at two or more study visits post drug treatment) and 33 of 56 patients developed neutralizing antibodies (Table 20). Due to the aforementioned drug interference issue, the sponsor reported incidence rate 4% is an underestimation.

In VDZ/PBO subjects, the incidence rate was around 2% (6/277) and 1% (3/277) at baseline and Week 6, respectively. During the maintenance, with the increasing clearance of vedolizumab from the body, the incidence rate increased to 17% (20/117) at Week 52 when vedolizumab levels were undetectable and no drug interference issue was expected (Table 21). However, since ADA could degrade during the long washout period, the incidence rate of 17% could still be an underestimation.

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

Yes. It appears that immunogenicity affects the serum concentrations of vedolizumab. Particularly, persistently positive ADA was associated with a substantial decrease in the serum concentrations of vedolizumab.

In Study C13006, the effect of ADA on pharmacokinetics was evaluated in patients treated with vedolizumab during the Maintenance Phase. In the ITT PK-evaluable Q8W group (n = 77), the mean trough concentration (at steady state [Week 46]) was 11.2 µg/mL. In the combined group of patients treated with the Q4W regimen (both ITT and non-ITT, n = 220), the mean trough concentration was 38.3 µg/mL. Two subjects with persistently positive ADA in the Q8W group (ITT) had trough levels much lower than the group mean: one was below the limit of quantitation (BLQ, 0.125 µg/ml) and the other was 4.17 µg/ml. In the non-ITT Q4W group, 3 patients were persistently ADA positive. Among these 3 subjects, 2 subjects had trough concentrations BLQ, and 1 patient had missing vedolizumab concentration.

In Study C13007, the mean trough level at steady state (Week 46) was 13.0 µg/ml (N=72) and 34.8 µg/ml (N=247) for Q8W and Q4W regimens, respectively. Serum concentrations were BLQ at Week 46 in 2 patients who were persistently ADA positive.

The impact of transient ADA on PK is less significant based on limited data. The mean steady state trough concentrations (Week 46) in the UC and CD subjects with transient ADA are 7.22 µg/ml (N=1) and 42.57 µg/ml (N=6) for Q8W and Q4W, respectively. It was noted that 4 subjects with transient ADA also had significantly reduced (<1 µg/mL, N=2) or undetectable (N=2) vedolizumab concentrations at Week 6.

2.3.3.3 Do the anti-drug antibodies have neutralizing activity?

Yes. The ability of ADA positive serum to neutralize the binding of vedolizumab to $\alpha_4\beta_7$ was examined using a validated flow cytometry binding competition assay. Fifty-nine percent (33 of 56) of the ADA-positive patients who received continuous vedolizumab in the maintenance phase developed neutralizing antibodies.

2.3.3.4 What is the impact of anti-drug antibodies on clinical efficacy?

Immunogenicity appeared to have negative impact on the efficacy of vedolizumab, particularly, in the subjects with persistent ADA.

In Study C13006, the 2 persistently ADA positive patients in the Q8W group both failed to achieve clinical remission in either induction (Week 6) or maintenance phase (Week 52 or early termination) although these two subjects were responders at Week 6. None of the 3 persistently ADA-positive patients in the Q4W group achieved clinical remission in either induction or maintenance phase and they were all non-responders at Week 6 as well.

In the Study C13007, none of the 3 patients who were persistent ADA positive achieved clinical remission in either induction or maintenance phase although one of them were responder at Week 6.

However, the small numbers of ADA positive patients preclude definitive conclusions regarding the impact of immunogenicity on the overall efficacy observed in the phase 3 studies.

2.3.3.5 What is the impact of anti-drug antibodies on clinical safety?

The small numbers of ADA positive patients (N=56) due to drug interference on immunogenicity assay preclude definitive conclusions regarding the impact of immunogenicity on the overall safety observed in the phase 3 studies.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

2.4.2 What are the drug-drug interactions?

Impact of Co-administered Drugs on Vedolizumab

No dedicated clinical studies were conducted to evaluate the effect of co-administered drugs on the pharmacokinetics of vedolizumab. The potential for concomitant immunomodulators therapies to impact vedolizumab's PK were evaluated using population pharmacokinetics approach based on data from phase 3 studies. The immunomodulator drugs were tested individually in the model: azathioprine, methotrexate, mercaptopurine, and aminosaliclates. The effect of co-medications on CL_L was not statically significant.

This observation was reflected in the 95% CI of co-medication's impact on CL_L contained 1 for all tested co-administered drugs (Table 22).

Table 22 Covariate Parameter Estimates From Final Population PK Model

Parameter	N (sam. / subj.) of subjects with Concomitant Medication	Estimate*	Bayesian 95% CI*
Categorical covariates (NULL effect = 1)	Total without Concomitant Medication: ~ 2554 (7.3)		
$CL_L \sim$ AZA full duration (θ_{16})	319 (13.9)	0.992	(0.958, 1.03)
$CL_L \sim$ MP full duration (θ_{18})	37 (9.8)	1.07	(0.97, 1.18)
$CL_L \sim$ MTX full duration (θ_{20})	32 (14.1)	1.02	(0.933, 1.11)
$CL_L \sim$ AMINO full duration (θ_{22})	> 600 (12.5)	1.02	(0.984, 1.06)

Source: Population PK and PD Report 2012, Table 8.

Abbreviations: AMINO = aminosalicylate concomitant therapy; AZA = azathioprine concomitant therapy; CL_L = clearance of linear elimination pathway; MP = 6-mercaptopurine concomitant therapy; MTX = methotrexate concomitant therapy; θ = fixed effect parameter.

* Parameter estimate and 95% CI were derived from the median, 2.5th and 97.5th quantiles of the Bayesian posterior probability distributions from 4 Markov Chain Monte Carlo (MCMC) chains.

Impact of Vedolizumab on Other Co-administered Drugs

The applicant didn't assess the potential of vedolizumab to impact PK of other co-administered drugs. As UC and CD involve chronic inflammation and is associated with an imbalanced cytokine network, indirect impacts on the formation of CYP450 enzymes cannot be ruled out. Therefore, the potential exists for an improvement in the inflammatory disease condition, e.g., upon treatment with vedolizumab, to indirectly impact the expression of CYP450 enzymes. So, the applicant needs to conduct studies to evaluate the DDI potential between vedolizumab and other CYP substrates in the UC and CD population.

2.4.3 What other co-medications are likely to be administered to the target population?

The standard approach to treat UC and CD is generally step-wise and directed, based on disease activity and the extent and location of disease. Initial treatment typically begins with anti-inflammatory agents, progressing to more potent therapies for patients who fail to demonstrate a response. Conventional pharmacologic treatments for these diseases include the 5-aminosalicylates (5 ASAs), corticosteroids, and immunomodulators (thiopurines such as azathioprine [AZA] and 6-mercaptopurine [6-MP]) for both UC and CD, along with methotrexate (MTX) for CD. In addition, standard practice often involves using these treatments in combination. Refer to Section 2.1.4 for drugs approved in the US for these same indications.

In addition to controlling inflammation, some medications may help relief of symptoms such as: antibiotics, anti-diarrheals, pain relievers, and iron supplements.

2.4.4 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

No.

2.5 General Biopharmaceutics

2.5.1 Was the manufacturing process changed during the development program? (Include a table listing all the products used throughout the clinical development programs.)

Yes. Three processes of vedolizumab have been used in nonclinical evaluations and in the clinical development program. Please refer to Table 2 for the products used throughout the development programs.

MLN002 Process A, also known as (b)(4) (LPD-02), was derived from an NS0 mouse myeloma cell line and was used in the early clinical and nonclinical studies. The subsequent MLN002 Process B and MLN002 Process C, also known as vedolizumab Process B and vedolizumab Process C, were derived from a Chinese hamster ovary (CHO) cell line. MLN002 (Process B) was the material used in the nonclinical studies. MLN002 Process C was the formulation used throughout phase 3 clinical trials and is the intended commercial material.

The comparability of Process B and Process C was evaluated in Study C13009. The study was a randomized, placebo-controlled, double-blind, parallel-group study where subjects were randomized in a 1:1:1 ratio to receive single IV doses of 600 mg Process B vedolizumab, 600 mg Process C vedolizumab, or placebo. All doses were administered as intravenous infusions lasting 30 minutes. The study was conducted in healthy male or female subjects, aged 19 to 45 years.

Six of these subjects were excluded from the PK analysis due to HAMA positivity (3 subjects) or due to having an inadequate PK profile (2 subjects). The statistical analysis of the observed drug concentration (C_{max}) and area under the drug concentration-time curve parameters comparing Process B and Process C is presented in Table 23.

Table 23 Summary of Statistical Analysis of Vedolizumab PK parameters in Study C13009 (geometric mean ratio and 90% CI)

Parameter

C_{max}

AUC_0

Source: Study C13009, Table 14.2.1.2A.

Abbreviations

C_m

The data indicated that the PK of the 2 processes meet the criteria for bioequivalence (i.e., the 90% CIs for the geometric mean ratios of AUC_{inf} and C_{max} fell within the range of 80% to 125%). Therefore, Process B and Process C drug products were considered comparable. This conclusion supports the pooling of data from studies 13002, 13006, 13007, 13009, and 13011 in population PK analysis. The comparability between Process A and Process B (or C) was not assessed. Given that all Phase 3 studies and critical PK/PD studies were conducted with Process B or C drug products, data from studies with Process A would not add value to the overall assessment of vedolizumab.

2.5.2 Was the proposed to-be-market formulation same as the formulation used in the pivotal clinical trials?

Yes. The to-be-market formulation was used in the pivotal phase 3 clinical studies.

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess therapeutic protein concentrations?

The assay used to determine the concentration of vedolizumab in the studies with Process B or Process C drug product was a direct capture ELISA. In this assay, a mouse anti-vedolizumab idiotypic antibody was immobilized on microtiter plates to capture vedolizumab. After blocking the wells, serum samples were added and bounded vedolizumab were detected with F(ab')₂ mouse anti-human immunoglobulin G (IgG) conjugated to horseradish peroxidase, followed by a colorimetric substrate. The lower limit of detection was 0.00125 µg/mL (0.125 µg/mL in undiluted serum) and the minimum required dilution was 100 (1% serum). The assay is considered acceptable and an overview of the assays performance is presented in Table 24.

Table 24 Vedolizumab PK Assay Methods and Performance

Report Title	Determination of MLN0002 in human serum by ELISA
Report Number	QPS 96-0622
Analyte Name	MLN0002
Sample Volume	5mL (Before 100x dilution, duplicate measurement)
Analytical Method Type	ELISA
Sample Processing Method	None
Calibration Range:	0.125 - 8 mcg/mL
Matrix QC Concentrations	0.125, 0.2, 1, 6.7, and 8 mcg/mL
QC Intra-batch Precision (%CV)	1.8% to 3.1 %
QC Intra-batch Accuracy (%Diff)	1.4% to 9.6%
QC Inter-batch Precision (%CV)	4.0% to 16.2%
QC Inter-batch Accuracy (%Diff)	-2.5% to 10.1%
Benchtop stability in human serum	26 hours at Room Temperature
Freeze/thaw Stability in human serum	5 cycles at Room Temperature/-70°C
Long-term Storage Stability in human serum	Long-term Storage Stability in human serum for 765 days at -70°C
Dilution Linearity	158 µg/mL diluted 100, 200, 300, 400, 500, 700, 800, 900, 1000
Selectivity (10 lots, spiked 0.2 and 6.7mcg/ml)	>75% lots tested within 100±20% Recovery

2.6.1.1 What is the range of standard curve? How does it relate to the requirements for clinical studies?

The range of the assay in assay buffer was from 0.00125 µg/mL to 0.08 µg/mL with a minimum required dilution of serum of 1:100, therefore the range of the assay was 0.125 µg/mL to 8 µg/mL for undiluted sample. Clinical samples with concentrations greater than 8 µg/mL were diluted within the calibration curve.

2.6.1.2 What are the lower and upper limits of quantitation?

The lower limit of quantification (LLOQ) of the assay was 0.125 µg/mL. The upper limit of the assay curve was 8 µg/mL

2.6.1.3 What are the accuracy, and precision at these limits?

The upper bound of intra assay precision and accuracy were 3.1% and 9.6%, respectively. The upper bound of inter assay precision and accuracy were 16.2% and 10.1%, respectively.

2.6.1.4 What is the sample stability under conditions used in the study?

Majority of the samples collected in the Phase 3 trials were within the stability date (765 days). In Study C13006, 54 of the 9905 (0.5%) received samples (including placebo) that were beyond the 765-day stability date. In Study C13007, 182 of 11927 (1.5%) received samples (including placebo) that were beyond the 765 stability date. No sample in Study C13011 was beyond stability.

2.6.1.5 What bioanalytical methods are used to assess the pharmacodynamic markers?

Binding Saturation: MAdCAM-1-Fc Binding Interference Assay

The MAdCAM-1-Fc Binding Interference Assay known as the “MAdCAM” assay was developed to demonstrate the presence of vedolizumab on the surface of cells bearing the $\alpha_4\beta_7$ integrin. MAdCAM-1-Fc is a fusion of human Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1) with the heavy and light chain Fc of a mouse monoclonal antibody. MAdCAM-1 is the natural ligand for the $\alpha_4\beta_7$ integrin. The basic principle of the assay is the following: (b) (4)

[Redacted text block]

As a result of assay validation, the assay demonstrated an overall intra-sample variability of 6% CV and an intra-subject variability of 20% CV. The assay is considered acceptable and further details of the assay characteristics are provided in Table 25.

Table 25 MAdCAM-1-Fc Binding Interference Assay Characteristics

Characteristic	Results
Limits of quantitation	Not applicable
Sensitivity	Saturation defined as <2% cells staining
Accuracy	Not applicable
Precision	9.8% for the CD4+CD45RO+ population (intra-assay <20%)

2.6.2 What bioanalytical methods are used to assess the immunogenicity?

2.6.2.1 What is the performance of the binding anti-drug antibody assay(s)?

The screening assay is a bridging assay designed to detect the presence of anti-vedolizumab antibodies in serum. This assay is not adequate as this assay had unacceptable drug tolerance (500 ng/mL), which is significantly lower than the mean trough vedolizumab concentrations following 300 mg Q8W (~ 10 µg/mL) or Q4W (~ 30 µg/mL) dosing regimen. A summary of the validation results is presented in Table 26 below. For more details, please refer to the CMC review by Dr. Qing Zhou.

Table 26 Screening Anti-Drug Antibody Assay Characteristics

Characteristic	Results
Limits of quantitation	Not applicable
Specificity	70% of blanks below cut point
Accuracy	Not applicable
Precision	Intrabatch < 5%, interbatch < 42% using PAHA positive control
Drug interference	Assay interfered with ≤ 500 ng/mL vedolizumab at 440 pg/mL HAHA, and up to 20 µg/mL vedolizumab at 5 µg/mL HAHA.

2.6.2.2 What is the performance of the neutralizing assay(s)?

Confirmed ADA-positive samples were further assessed for the ability of the ADA to neutralize the binding of vedolizumab to cells. A competitive flow cytometry-based assay was designed to determine the ability of the immune serum to inhibit the binding of labeled vedolizumab to an $\alpha_4\beta_7$ -expressing cell line. This assay is not adequate as this assay had unacceptable drug tolerance (100 ng/mL), which is significantly lower than the mean trough vedolizumab concentrations following 300 mg Q8W (~ 10 µg/mL) or Q4W (~ 30 µg/mL) dosing regimen. A summary of the validation results is presented in Table 27 below. For more details, please refer to the CMC review by Dr. Qing Zhou.

Table 27 Neutralizing Anti-Drug Antibody Assay Characteristics

Characteristic	Results
Limits of quantitation	Not applicable
Specificity	S/N ratio for negative >10
Accuracy	Not applicable
Precision	Intra-assay < 6%, Inter-assay < 20% using positive control
Drug interference	Assay is interfered with 100 ng/mL vedolizumab with the low positive control and 1 µg/ml vedolizumab for the high positive control.

3. APPENDIX

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

Ulcerative Colitis:

1.1.1 Is there evidence of effectiveness for the induction of clinical response and remission?

- Does the Dose/Exposure-response relationship for efficacy support the proposed dose of 300 mg at Weeks 0 and 2 in the Induction phase?

A significant exposure-response relationship for clinical response and remission in the induction phase provides supportive evidence of effectiveness. Furthermore, exposure-response analysis (**Figure 1**) indicates that higher dose may provide additional benefit in the induction phase. However, considering totality of evidence presented in the application for both induction and maintenance phases, the proposed dose of 300 mg at Week 0 and 2 in the induction phase appears reasonable for regulatory approval. We recommend sponsor to explore the possibility of higher doses in the induction phase (post-approval) with an aim to achieve higher responder rate.

The rate of clinical response at Week 6 (primary endpoint) for vedolizumab treatment was 47.1% versus 25.5% in the placebo group, with a difference of 21.7% (95% CI: 11.6, 31.7; $p < 0.0001$). The difference from placebo in remission rate at Week 52 (primary end point) was 26.1% (95% CI: 14.9, 37.2) for Q8W (300 mg vedolizumab dosed Q8W) and 29.1% (95% CI: 17.9, 40.4) for the Q4W dosing group. It is important to note that the efficacy of vedolizumab for both induction and maintenance therapy was consistently observed, independent of underlying demographic factors and disease characteristics, such as age, gender, disease location, baseline severity of disease, previous TNF α antagonist use, previous treatment failure, and concomitant medications at baseline.

From two dose-ranging Phase 2 studies C13002 and M200-022, and within each study there was no apparent dose-response relationship observed. The data for clinical response at day 43 of both studies are summarized in **Table 1**. Note that C13002 and M200-022 were using the product manufactured with the commercial process (Process C) and clinical trial process (Process B) respectively. No comparison of the results between these two studies is to be made. Also, there are differences between the Phase 2 and Phase 3 studies with respect to study design (small number of patients), study population (Phase 2 studies have patients with mildly active UC), and clinical endpoint which makes the determination of the adequacy of induction dose challenging.

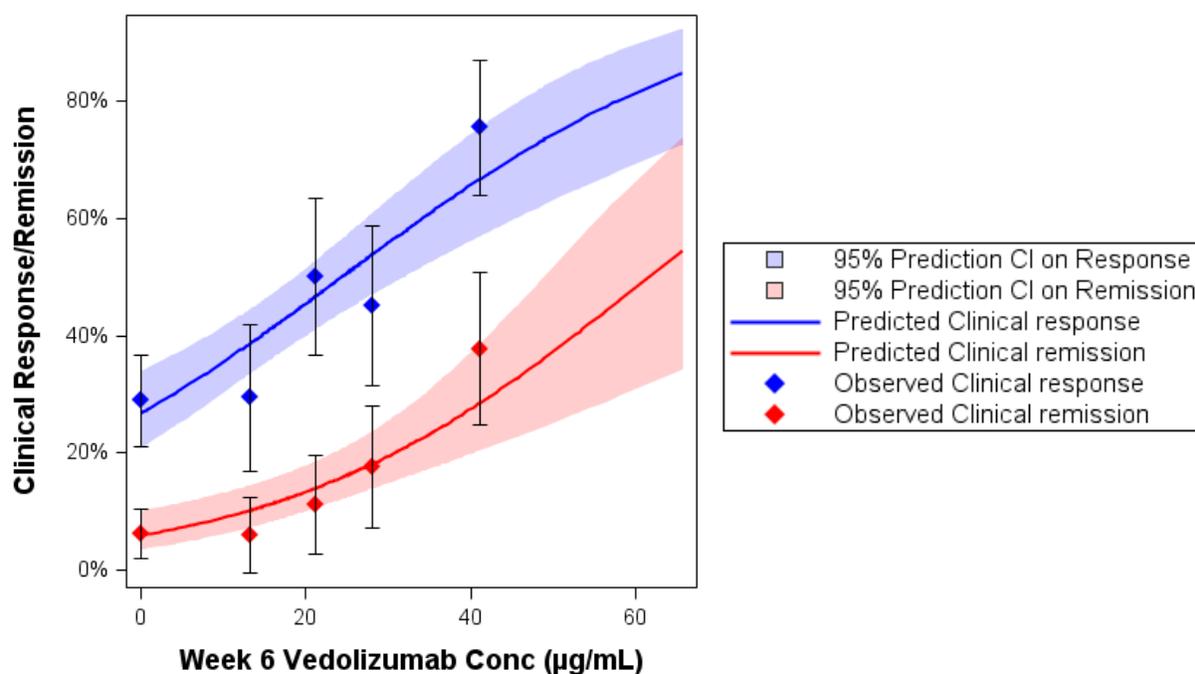
Table 1. Phase 2 Dose-Response for Efficacy Show Similar Response Across Dose Groups

Study	M200-022		C13002		
Dose	0.5 mg/kg N = 58	2 mg/kg N = 60	2 mg/kg N = 12	6 mg/kg N = 14	10 mg/kg N = 11
*Clinical Response at Day 43	38 (66%)	32 (53%)	6 (50%)	9 (64%)	6 (55%)

- Clinical Response measured by UCCS (M200-022) and Partial Mayo Score (C13002), respectively.

Therefore exposure-response analysis was conducted using the data from the registration Phase 3 trial (C13006). Significant relationships were established between clinical response or remission at Week 6 (induction phase) with vedolizumab Week 6 trough concentration using logistic regression. **Figure 1** demonstrates the exposure response relationship for clinical remission at Week 6 depicting that higher exposures may be associated with higher efficacy.

Figure 1. Exposure-Response relationships for Clinical Response and Remission at Week 6 with Week 6 Vedolizumab Trough Concentrations ((Study C13006).



However, it is possible that the exposure-response relationships are confounded by several risk factors, such as prior exposure to anti-TNF α therapy, previous treatment failure, and concomitant

medications at baseline. Distributions of these factors are not balanced across the concentrations quartiles at Week 6 (Table 2). For example, higher clinical remission in the patients with fourth quartile of concentrations may also be driven by the fact that there were less proportion of patients that had failed anti-TNF α therapy and higher proportion of patients with baseline concomitant immunomodulator use in the highest quartile.

Table 2. Distribution of Risk Factors by Concentration Quartiles at Week 6 (Study C13006, Intent-to-Treat Population)

Risk factors	Placebo (N=137)	Mean level in each Concentration Quartile			
		1 (N=53)	2 (N=52)	3 (N=55)	4 (N=54)
VDZ Concentration (range) at Week 6 ($\mu\text{g/mL}$)	0	11 (0 - 17)	21 (17 - 25)	28 (25 - 33)	44 (33 - 66)
Age	41	44	39	39	39
Gender (Male)	65%	58%	69%	62%	41%
Baseline Mayo Sore	9	9	8	9	8
Baseline Fecal Calprotectin (mg/kg)	2360	3495	2060	2595	2363
Albumin (g/L)	37	36	38	39	41
Previous Exposure to TNF α antagonist	50%	49%	48%	47%	22%
Prior TNF α antagonist Failure	42%	43%	38%	42%	20%
Baseline Concomitant Immunomodulator Use	31%	28%	23%	38%	43%

Considering the imbalance in risk factors, multivariate logistic regression was also conducted to account for potential confounding factors like baseline mayo score, albumin level, prior immunomodulator use and prior TNF alpha failure status. Exposures were still significant after adjusting for these factors indicating that higher dose or exposure may provide additional benefit.

Mean pharmacokinetic simulations were performed for the proposed dosing regimen and two other alternate dosing regimens with increased dosing frequency to examine the magnitude of increase in exposure at week 6. Simulated mean trough concentration at Week 6 increases by ~2-fold with an additional 300 mg dose at Week 4, and ~2.5-fold with additional two doses at Week 1 and 4 (**Figure 23**). See Section 4.4.1.1 for further description of the simulation results.

However, there is one important aspect of induction of response that is worth considering while evaluating the adequacy of the proposed dose in the induction phase. There is an evidence to suggest that there may be a delay in achieving response in the induction phase with vedolizumab indicating that measuring clinical response or remission at Week 6 may be early. Sponsor conducted an analysis showing that among patients who failed to demonstrate response at Week 6, delayed clinical response was observed at Weeks 10 and 14 for greater proportions of vedolizumab patients (25.0% and 27.2%, respectively) compared with placebo patients (14.6% and 20.7%, respectively) (**Table 3**). These results indicate that patients who did not initially respond to treatment by Week 6 may benefit from an additional 4 to 8 weeks of treatment.

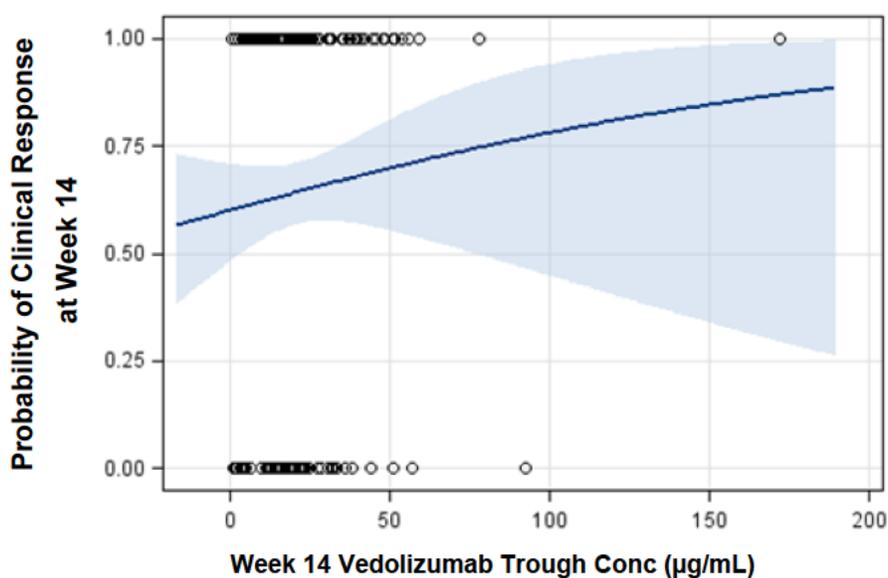
Table 3. Delayed Response Population (Clinical Response by Partial Mayo Score at Week 10 and 14 in Non-Responders at Week 6)

Clinical Response ^b	Week 6 Nonresponders			
	Induction Cohort 1 ITT Population		Induction Cohort 2 Open-label	VDZ (Combined)
	PLA N = 82 ^a	VDZ N = 92 ^a	VDZ N = 230 ^a	N = 322 ^a
Clinical Response ^b at Week 10				
n (%)	12 (14.6)	23 (25.0)	79 (34.3)	102 (31.7)
95% CI	(7.0, 22.3)	(16.2, 33.8)	(28.2, 40.5)	(26.6, 36.8)
Clinical Response ^b at Week 14				
n (%)	17 (20.7)	25 (27.2)	101 (43.9)	126 (39.1)
95% CI	(12.0, 29.5)	(18.1, 36.3)	(37.5, 50.3)	(33.8, 44.5)

(Source: Sponsor's Clinical Study Report for Trial C13006, Table 14.3.1.17M)

In addition analysis was performed by the FDA reviewer to explore relationship between clinical response and trough concentration at Week 14. No exposure-response was evident, indicating that exposures achieved by Week 14 may be adequate to achieve clinical response at Week 14 (Figure 2).

Figure 2. No Significant Exposure-Response Relationship for Clinical Response at Week 14 (Study C13006)



In addition, sponsor conducted a trial C130011 in Crohn's disease patients which also provides evidence of delayed response. With an additional Week 6 dose of vedolizumab, the difference in clinical remission over placebo increased from 6.9% to 15.5%, from Week 6 to Week 10. Induction therapy beyond 6 weeks may provide additional benefit because pharmacologic inhibition of lymphocyte migration to the gut may require a longer timeframe for optimal induction efficacy for patients who have failed TNF α antagonists. Even though Crohn's disease is a different disease but still falls under the umbrella of inflammatory bowel diseases. This finding serves as supportive evidence that a delayed response phenomenon may be associated with vedolizumab.

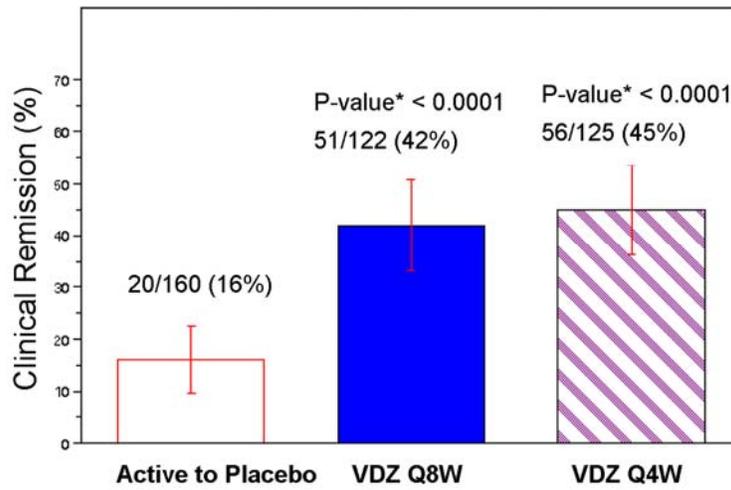
Considering all of the arguments as described above, it is quite possible that increasing the dose may result in more responders in the induction phase thereby increasing the rate of clinical remission at Week 52. It may also be that since there is an evidence of delayed response, Week 6 may not be the optimal time point to explore exposure-response relationships. Therefore, we agree with the sponsor proposed dosing regimen but recommend them to explore option of higher induction doses post-approval.

1.1.2 Does the Dose/Exposure-response relationship for efficacy support the proposed 300 mg every 8 weeks in the maintenance phase?

Yes. The proposed dose and dosing interval is acceptable. Based on the results from the pivotal trial C13006, the efficacy of both Q8W and Q4W dosing regimen was significantly higher than placebo. However, there appears to be no additional clinical benefit with Q4W compared to Q8W dosing regimen (**Figure 3**). The magnitude of clinical benefit were found similar between the Q8W and Q4W vedolizumab regimens, as demonstrated by clinical meaningful results for the primary endpoint (clinical remission at Week 52). Furthermore, when the data was visualized longitudinally based on partial mayo score, it is evident that both Q4W and Q8W dosing regimen provide similar clinical benefit over time (**Figure 4**).

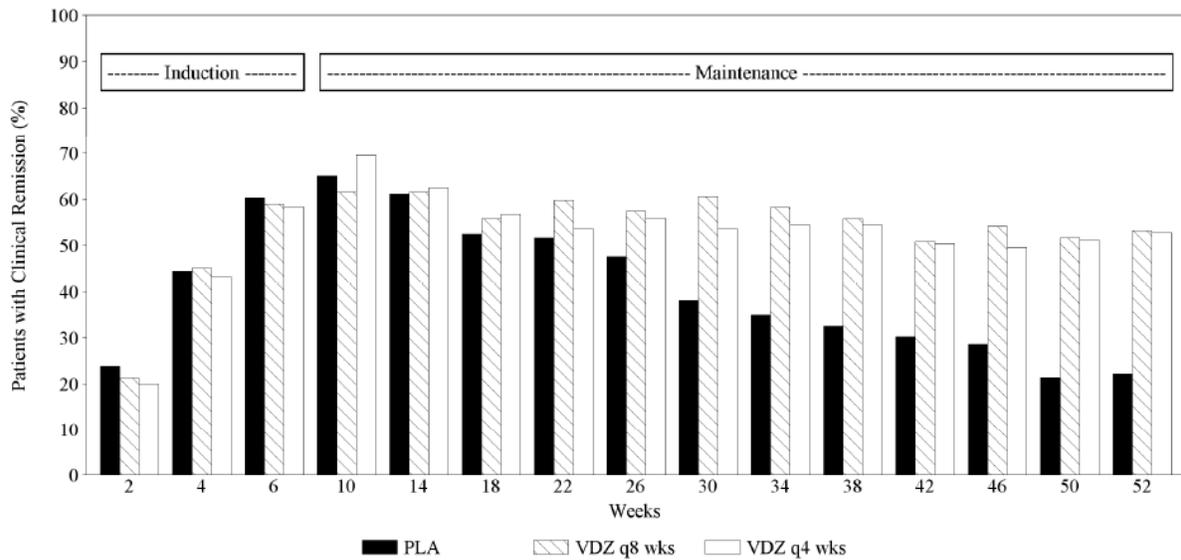
Sponsor also evaluated other exploratory endpoints (time to disease worsening and treatment failure). Disease worsening was defined as an increase in partial Mayo score of ≥ 3 points from the Week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 6 value > 6) and a partial Mayo score ≥ 5 points. Treatment failure was defined as disease worsening, need for rescue medications or surgical intervention for treatment of UC, or study drug-related AE leading to discontinuation from the study. Based on these endpoints, there appears to be no difference between Q4W and Q8W dosing regimen (**Figure 5** and **Figure 6**).

Figure 3. Clinical Remission (95% CI) by Treatment Group at Week 52 (Study C13006)



(Source: Sponsor's Clinical Study Report for Trial c13006, Figure 14.3.1.2DM)

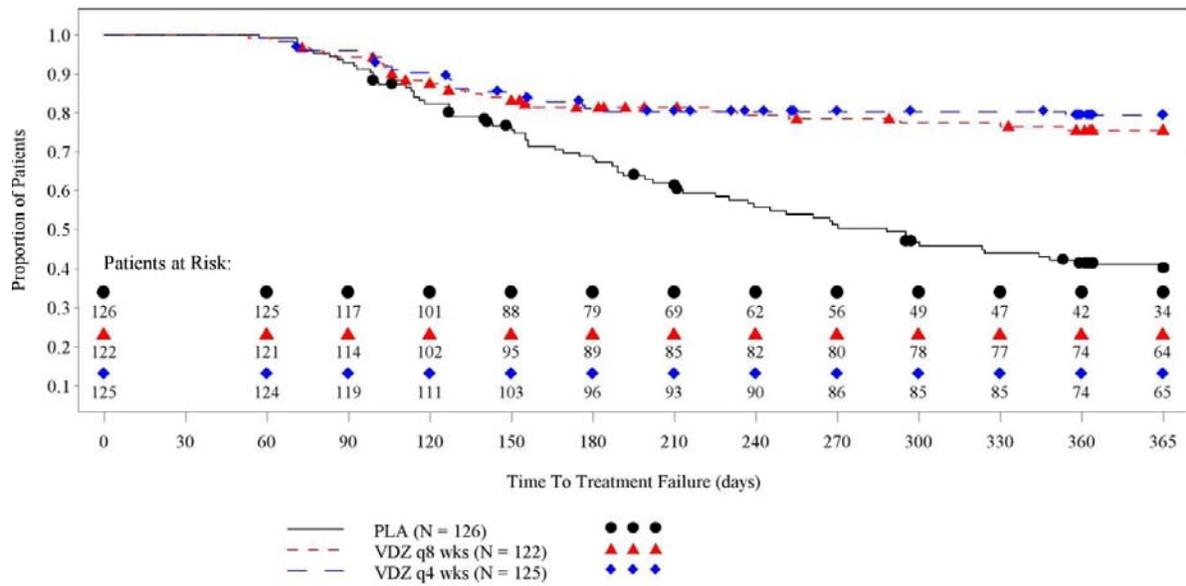
Figure 4. Clinical Remission on Partial Mayo Score by Study Visit (Study C13006)



- PLA (Active-to-placebo group): responders at Week 6 and re-randomized to placebo group in the maintenance phase

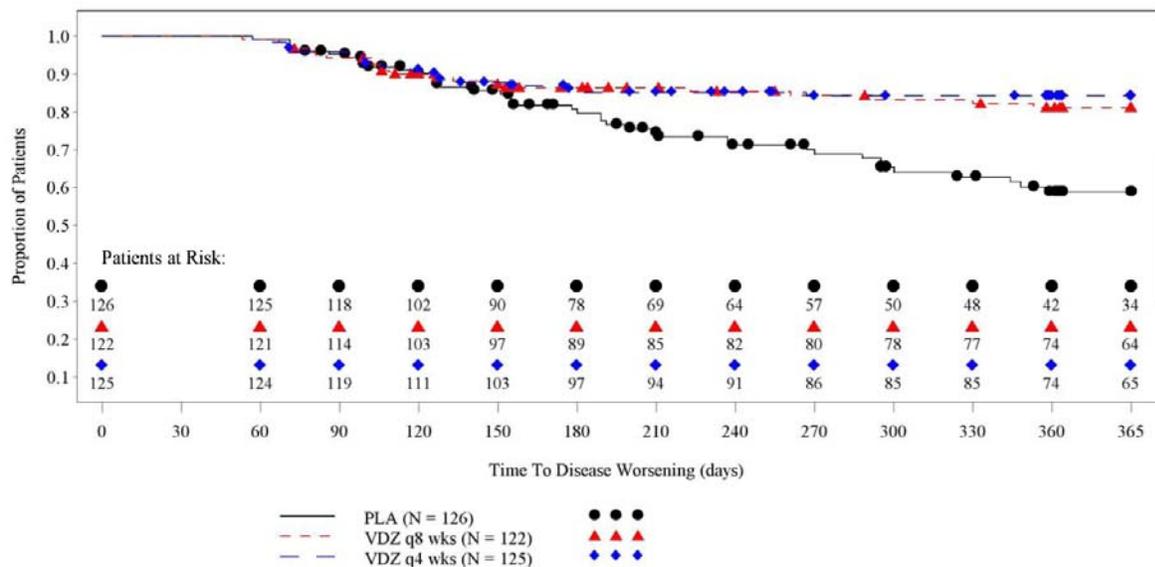
(Source: Sponsor's Clinical Study Report for Trial c13006, Figure 14.3.1.25BM)

Figure 5. Kaplan Meier Survival Curve of Time to Treatment Failure (Study C13006)



- PLA (Active-to-placebo group): responders at Week 6 and re-randomized to placebo group in the maintenance phase
(Source: Sponsor's Clinical Study Report for Trial c13006, Figure 14.3.1.19BM)

Figure 6. Kaplan Meier Survival Curve of Time to Disease Worsening (Study C13006)



- PLA (Active-to-placebo group): responders at Week 6 and re-randomized to placebo group in the maintenance phase
(Source: Sponsor's Clinical Study Report for Trial c13006, Figure 14.3.1.19AM)

1.1.3 Is there evidence to support increase dosing frequency from Q8W to Q4W if lack or decrease of response?

No. The sponsor has not demonstrated that dose escalation from Q8W to Q4W will result in greater efficacy.

Sponsor is proposing that some patients who did not benefit from the Q8W regimen derived benefit from more frequent dosing with the Q4W regimen. The evidence was that 32 patients who discontinued from vedolizumab Q8W dosing, predominantly due to lack of efficacy, and transitioned to Q4W dosing in Study C13008 showed a clinical remission rate of 6% (2/32) at Week 0 that increased to 25% (8/32 patients) at Weeks 28 and 52.

However, without a comparative arm receiving subsequent treatment with Q8W it is not possible to discern whether the additional benefit was due to additional time on treatment or the higher dosing frequency. Furthermore, based on the randomized comparison of two doses in the maintenance phase, there appears to be no additional benefit for the Q4W regimen compared to Q8W. Taken together, the sponsor did not provide sufficient data to support dosing interval adjustment from Q8W to Q4W in the case of a lack of and/or decrease in response

1.1.4 Is the response observed at Week 14 predictive of that at Week 52? (“Reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14”?)

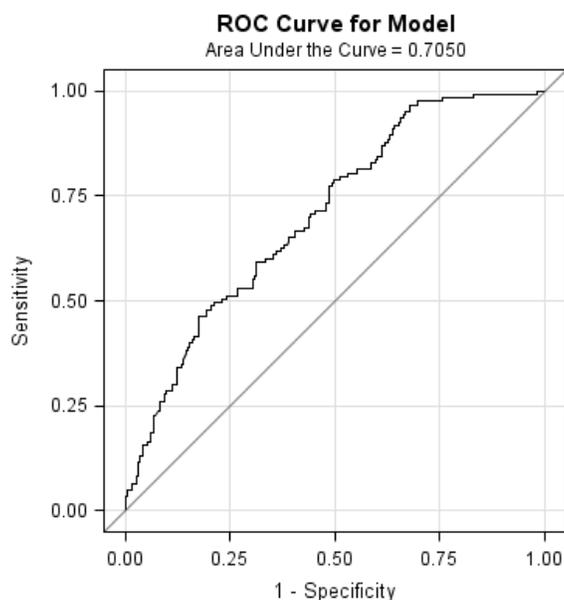
Yes. The sponsor’s proposed labeling statement to “reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14” appears reasonable.

The analysis was conducted for two groups of patients. One is vedolizumab treated patients who did not obtain response up to Week 14 (Sustained Non-Response at Week 14). The other is vedolizumab treated patients who responded initially at Week 6 but lost response at Week 14.

Of 198 patients in the first group, only 10 (4%) remitted by Week 52. Of 53 patients in the second group, only 2/28 (7%) and 2/25 (8%) remitted by Week 52 in Q8W and Q4W. These rates are lower than the remission rate of 19.5% in the placebo group of Study C13006 at Week 52. The low remission rates support sponsor’s statement by suggesting that for non-responders at Week 14, it is unlikely that they would regain any additional benefit afterwards, regardless of their response status before Week 14.

Logistic regression analyses were also conducted to evaluate the predictive capability of overall clinical response at Week 14 for the probability of remission at Week 52. The ROC curves for these analyses are shown in **Figure 7**. The area and the curve ratio (0.62 and 0.71) and p-value ($p < 0.0001$) suggest a good predictive capability of clinical response at Week 14.

Figure 7. ROC curves for the predictive capability of clinical response at Week 14 for the probability of clinical remission at Week 52 (Study C13006).

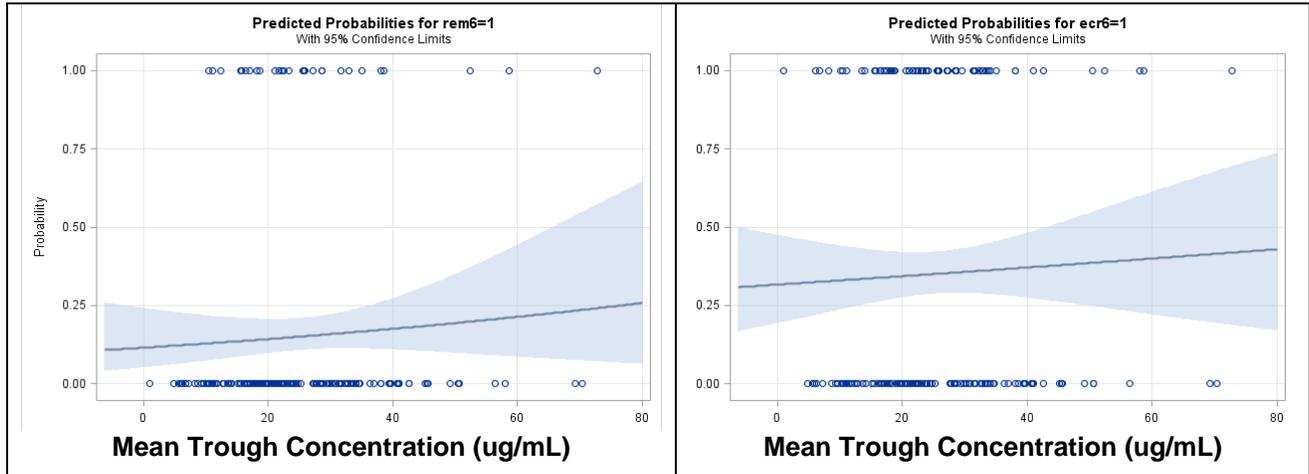


Crohn's Disease:

1.1.5 Do the dose/exposure-response relationships for efficacy support the proposed dose of 300 mg at weeks 0 and 2 in the Induction phase?

Yes, the proposed dose appears reasonable. No dose-response data are available for the induction phase from either the phase 2 or phase 3 trials, at the proposed doses. Additionally exposure-response was not evident for the induction of clinical remission or enhanced clinical response at week 6 (primary efficacy end points), based on mean trough concentrations at week 6. Exposure-response analyses consisted of both univariate and multivariate logistic regressions to account for potential confounding factors. In no case was the mean trough concentration a significant predictor of clinical remission or enhanced clinical response. Further details on the multivariate logistic regression results are shown in Section 4.4.2. Results of the univariate analysis testing clinical remission and enhanced clinical response as a function of mean trough concentration are shown in Figure 8.

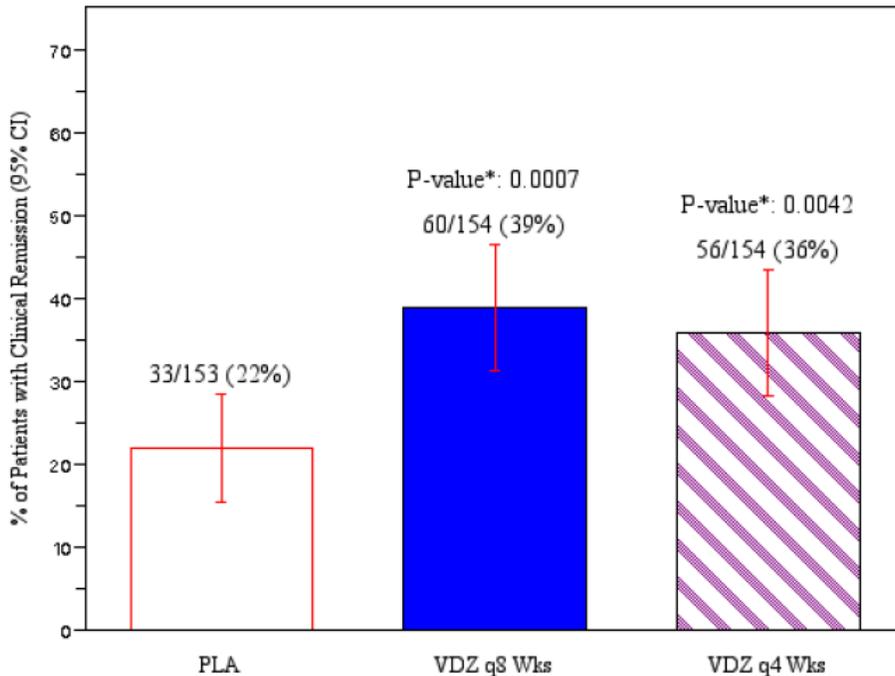
Figure 8. No significant exposure-response relationship for clinical remission (left panel) or enhanced clinical response (right panel) at week 6 in study c13007.



1.1.6 Do the dose/exposure-response relationships for efficacy support the proposed dose of 300 mg every 8 weeks in the maintenance phase?

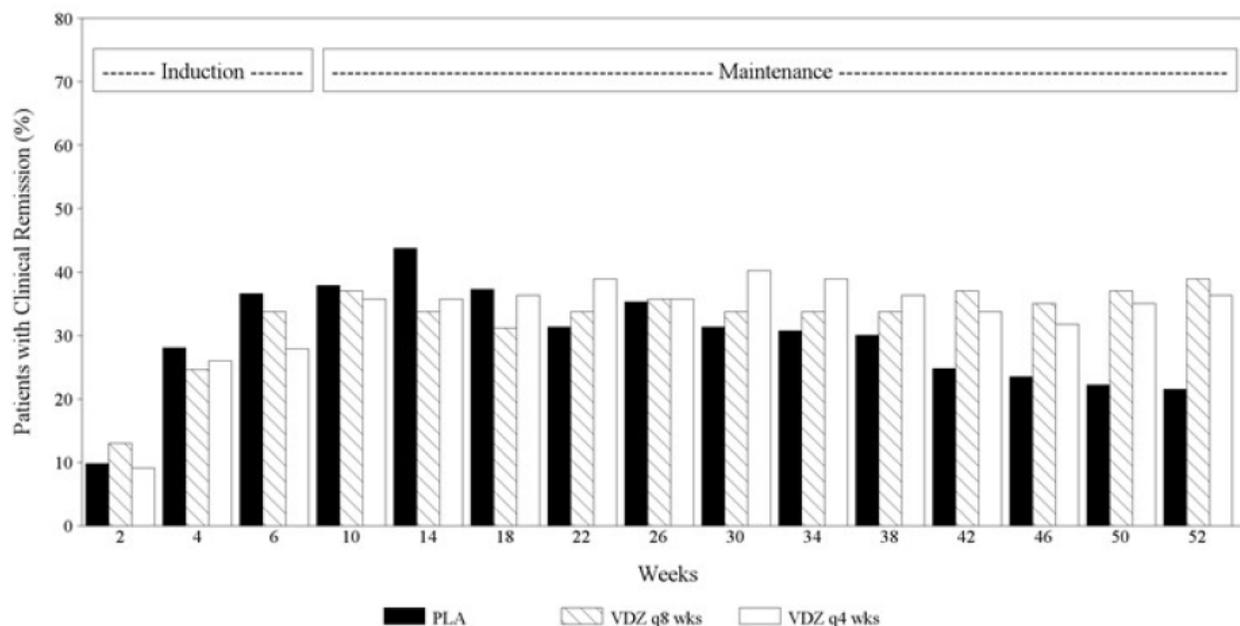
Yes, the proposed maintenance dose of 300 mg every 8 weeks is acceptable. There is no dose-response for efficacy observed between the Q8W and Q4W dosing intervals (Figure 9, Figure 10). Additionally, exposure-response analyses including both univariate and multivariate logistic regressions, do not indicate a relationship between mean trough concentration and the probability of achieving clinical remission or enhanced clinical response at week 52 (Figure 11).

Figure 9. No dose-response was observed in clinical remission at week 52 for the Q4 and Q8 weekly dosing arms of trial c13007.



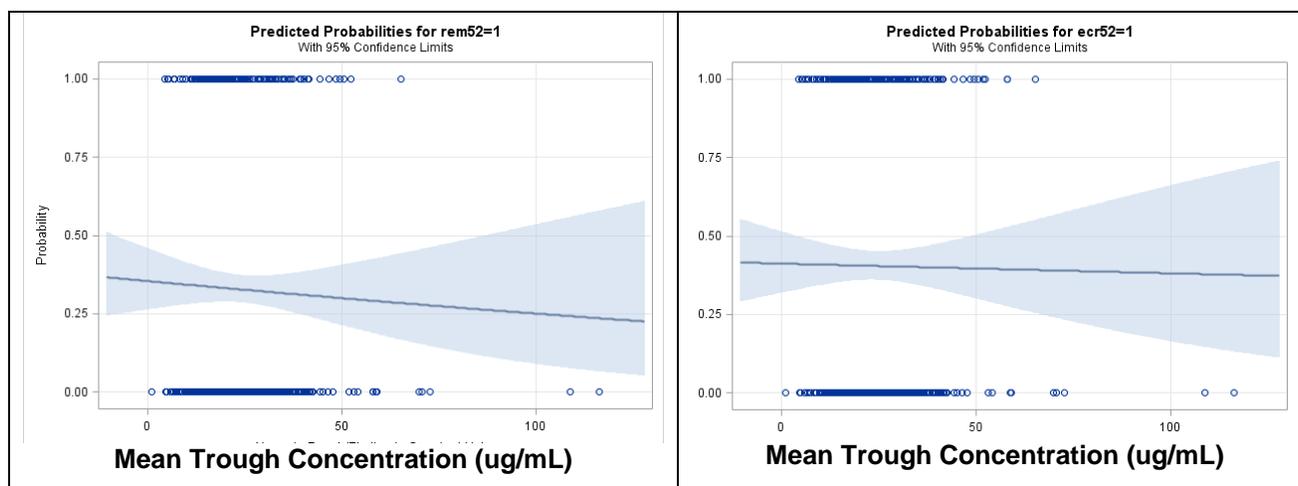
(Source: Sponsor's Clinical Study Report for Trial c13007, Figure 10)

Figure 10. No Dose Response is evident between the Q4W and Q8W dosing regimens in trial c13007.



(Source: Sponsor’s Clinical Study Report for Trial c13007, Figure 25)

Figure 11. No significant exposure-response relationship for clinical remission (left panel) or enhanced clinical response (right panel) at week 52 in study c13007.



1.1.7 Is there evidence to support increasing the dosing frequency from Q8w to Q4w if there is a lack of response or decrease in response?

No. The sponsor has proposed increasing the dose in patients who exhibit a decrease in response or lack of response. However, their data was not studied in such a way that this claim can be supported. The sponsor is claiming that data from patients that were considered treatment failures due to lack of efficacy in the Q8 weekly dose group and subsequently enrolled in study

c13008 (n=57) to receive vedolizumab Q4 weekly provided evidence of additional benefit -- 32% (n=18) of these patients achieved remission by week 52. The argument against this is based on the fact that this was not a controlled assessment. That is, there was no comparison to subsequent treatment with Q8 weeks. Therefore, it is not possible to discern whether the additional benefit was due to additional time on treatment or the higher dose.

1.1.8 Is the response observed at Week 14 predictive of that at Week 52? (i.e. Should the label state: (“Reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14”?)

Yes, the sponsor’s statement in the proposed label to “reconsider continuation of therapy in patients who show no evidence of therapeutic benefit by Week 14” is reasonable. Of the patients that did not obtain remission at week 14 (n = 98 for Q8W and n=91 for Q4W), 18% (n=18) remitted by week 52 for the Q8W dose group and 22% (n=20) remitted by week 52 for the Q4W dose group (Shown in Figure 12). These rates are lower than the remission rate of 21.6% in the placebo group of Study C13007 at Week 52. A univariate and multivariate logistic regression analysis was also done to evaluate the predictive capability of remission at week 14 for the probability of remission at week 52. The Receiver Operating Characteristic (ROC) curves for these analyses are shown in Figure 13. In the case of the multivariate analysis, the occurrence of remission at week 14 had the highest significance of any of the model covariates with a p-value < 0.0001. See Section 4.4.2.1 for further description of the model results.

Figure 12. If remission is not achieved by week 14, there is an 18 – 22% chance that subject will remit by week 52

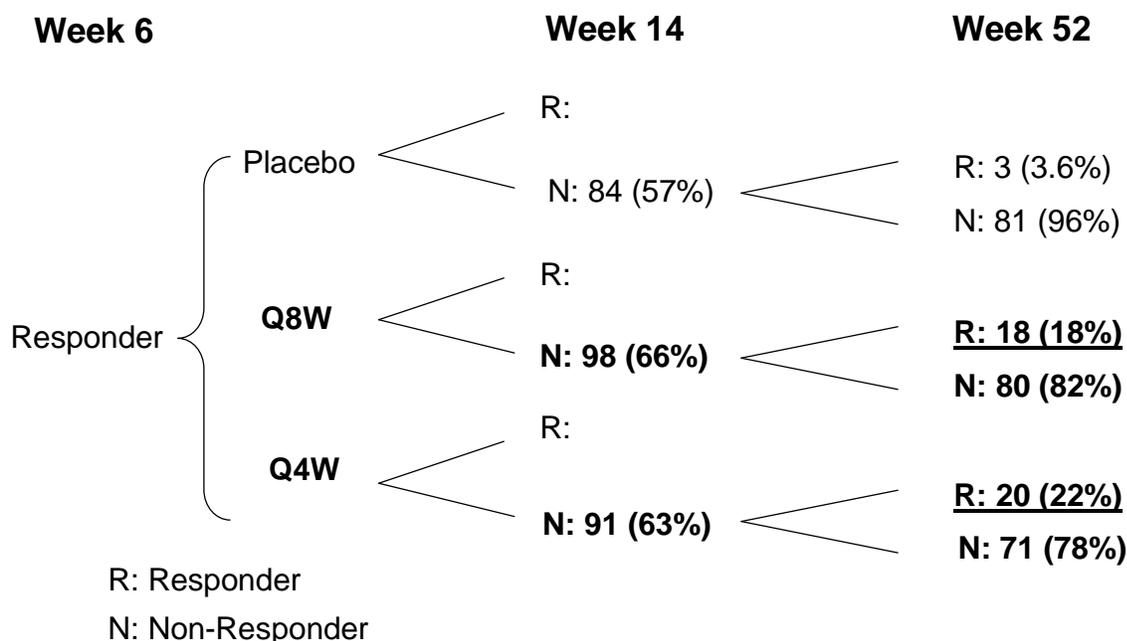
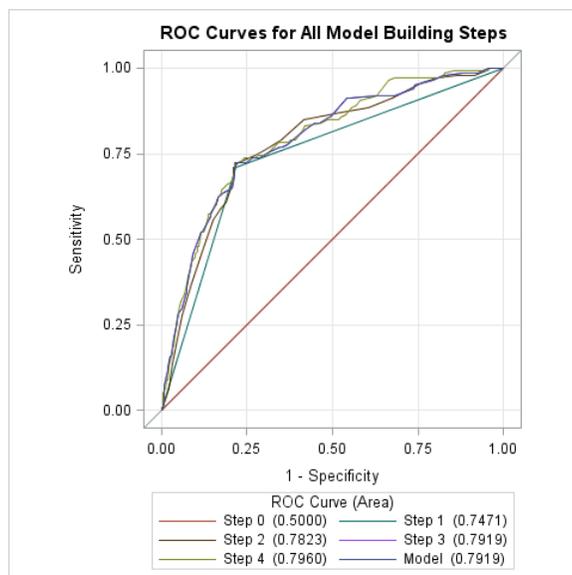


Figure 13. ROC curves for the predictive capability of clinical remission at week 14 for the probability of clinical remission at week 52. The graph depicts results for the multivariate analysis. Steps 1-4 and ‘model’ are the ROC curves for each step of the model building procedure which consisted of forward selection of 4 covariates (clinical remission at week

14, baseline HBI, concomitant immunomodulator use, and concomitant corticosteroid use) and the backward elimination of concomitant corticosteroid use. The final model ROC curve is indicated by the dark blue line.



1.2 Recommendations

Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this BLA from a clinical pharmacology perspective and recommends approval. Considering a significant exposure-response relationship observed for induction of clinical response and clinical remission in the induction phase for UC patients, we have the following recommendation for the sponsor:

- Explore higher induction doses for vedolizumab for induction of clinical response with ulcerative colitis and remission in UC. This can be accomplished by either increasing the total dose or changing the dosing frequency to have additional vedolizumab doses between Week 2 and 6. Crohn's disease.

1.3 Label Statements

Labeling recommendations and edits will be discussed under an addendum to this review.

2 PERTINENT REGULATORY BACKGROUND

Takeda is seeking FDA approval for vedolizumab, a humanized monoclonal antibody, for the treatment of patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD). Vedolizumab is classified as an integrin receptor antagonist.

The sponsor is providing data from 19 clinical studies from sites in Europe and North America, including 197 healthy subjects and 3129 patients with inflammatory bowel disease (1279 patients with UC and 1850 patients with CD). Trial c13006 in patients with moderate to severely active UC succeeded to meet its primary endpoints of clinical response at 6 weeks and clinical remission at 52 weeks. Whereas the pivotal CD trial (c13007) failed to meet one of the two primary efficacy endpoints. The primary endpoint of clinical remission was met for both the 6 Week and 52 Week evaluations. However, the primary endpoint of enhanced clinical remission

was incorporated into the trial after enrollment had begun as a non-co primary endpoint. Enhanced clinical response was not different from placebo at Week 6, however, was statistically superior to placebo at weeks 10 and 52.

Vedolizumab is second in its class of integrin receptor antagonists to natalizumab. As such the concern for progressive multifocal leukoencephalopathy (PML), associated with natalizumab use, is a relevant discussion regarding the safety of this drug. Unlike natalizumab, the sponsor claims vedolizumab only binds to the alpha-4, beta-7 integrin receptor, which is thought to be gut specific. Whereas natalizumab also binds to the alpha-4, beta-1 integrin receptor which is thought to be located on endothelial cells and its inhibition is thought to be related to PML. Thus, vedolizumab's selectivity to the alpha-4, beta-7 integrin receptor may relieve the concern for PML. See the clinical review by Dr. Laurie Muldowney and December 12th DGIEP Advisory Committee Meeting Minutes for further details.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Ulcerative Colitis

The evidence for efficacy of vedolizumab for the treatment of UC is predominantly based on the results of Study C13006, a phase 3, multinational, randomized, double-blind, placebo-controlled trial. This study separately evaluated the efficacy and safety of vedolizumab for 1) induction and, then, 2) maintenance of remission in patients with moderately to severely active UC. The efficacy of vedolizumab for induction therapy in UC demonstrated in Study C13006 is supported by Study M200-022, the phase 2, randomized, double-blind, placebo-controlled, proof-of-concept study in 181 patients with active UC, which demonstrated the efficacy of vedolizumab (0.5 and 2.0 mg/kg) to induce clinical remission (treatment differences of 19% ($p = 0.017$) and 18% ($p = 0.023$), respectively). Unique to this program, Study M200-022 also provides important histopathological evidence of decreased inflammation in biopsies of diseased colon during vedolizumab treatment. In addition, an ongoing, open-label, single-arm, longterm extension safety study (Study C13008) is also evaluating the persistence of efficacy with continued vedolizumab treatment in patients with UC.

3.1.1 Ulcerative Colitis: Induction and Maintenance Study Design of C13006

Study C13006 evaluated both induction and maintenance therapy. The Induction and Maintenance Studies within Study C13006 were powered separately and had distinct patient populations, endpoints, and statistical analyses. The total duration of therapy in Study C13006 was 52 weeks, which consisted of a 6-week induction period followed by a 46-week maintenance period.

There were 2 sequential Induction Phase cohorts of enrolled patients. Eligible patients enrolled in Cohort 1 were randomized in a 3:2 ratio to double-blind vedolizumab 300 mg or placebo administered intravenously. The number of patients enrolled into Cohort 1 was determined by the sample size requirements for the Induction Study efficacy analyses. After Cohort 1 enrollment was completed, additional patients were enrolled into Cohort 2, in order to provide sufficient numbers of patients to fully power the Maintenance Study efficacy analyses. All patients in Cohort 2 received open-label vedolizumab, administered at a dose of 300 mg at Weeks 0 and 2.

Efficacy was assessed at Week 6 for all patients. The Induction Study efficacy analyses were based on the assessments performed on patients included in the randomized, double-blind treatment groups in Cohort 1. Safety analyses for the Induction Phase include all safety data collected from baseline (Week 0) through the Week 6 induction assessments, summarized by Induction Phase treatment group.

The Maintenance Phase began after the Week 6 efficacy assessments and continued through Week 52. Patients who completed the Induction Phase (either cohort) were enrolled into the Maintenance Phase. The maintenance treatment group assignment was based on both the Week 6 treatment response and the induction treatment assignment. At Week 6, vedolizumab-treated patients in both Cohorts 1 and 2 who had achieved clinical response (as defined by the protocol and assessed by the investigator) were randomized in a 1:1:1 ratio to one of the following blinded maintenance regimens: vedolizumab 300 mg Q4W, vedolizumab 300 mg every 8 weeks

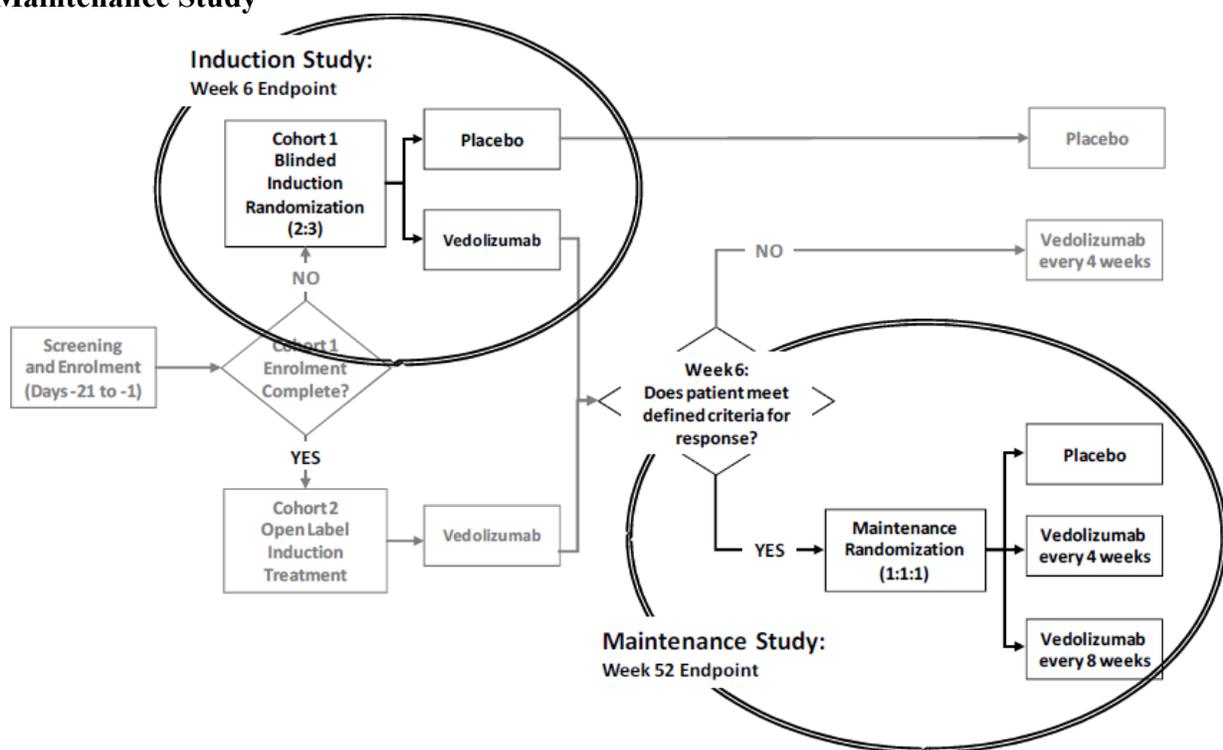
(Q8W), or placebo. These patients comprise the Maintenance ITT population, the primary efficacy population.

Patients in Induction Phase Cohorts 1 and 2 who had received vedolizumab induction treatment and had not achieved clinical response at Week 6 were assigned to receive vedolizumab every 4 weeks from Week 6 through Week 52. These patients contribute to the non-ITT population of the Maintenance Phase.

Patients in Induction Phase Cohort 1 who had been randomized to placebo were assigned to continue receiving placebo from Week 6 through Week 52. These patients also contribute to the non-ITT population of the Maintenance Phase.

In **Figure 14**, the treatment arms that provided data for the efficacy analyses for the Induction Study and the Maintenance Study are shown.

Figure 14. Treatment Arms Contributing to Efficacy Analyses in the Induction and Maintenance Study



(Source: Sponsor's Clinical Overview, Figure 4-1)

The primary endpoint for the Induction Study, the proportion of patients with clinical response at Week 6, was met, with statistical significance. Patients who received vedolizumab induction treatment were significantly more likely to achieve a clinical response at Week 6 compared to patients who received placebo. Of the 225 patients who received vedolizumab treatment, 106 (47.1%) achieved a clinical response at Week 6 compared with 38 of 149 patients (25.5%) who received placebo. The difference from placebo was 21.7% (95% confidence interval [CI]: 11.6, 31.7; $p < 0.0001$), with a relative risk of 1.8 in favor of vedolizumab.

Subgroup analyses reinforce the consistency of the effect of vedolizumab induction treatment. The efficacy of vedolizumab for induction therapy was consistently observed, independent of underlying demographic factors and disease characteristics, such as age, gender, disease location, baseline severity of disease, previous TNF α antagonist use, previous treatment failure, and concomitant medications at baseline.

The primary and all 4 key secondary endpoints of the Maintenance Study were met for both vedolizumab dosing regimen groups, with statistical significance. The primary endpoint for the Maintenance Study, the proportion of patients with clinical remission at Week 52, was positive. The clinical benefit of vedolizumab was evident in the significantly higher remission rates for vedolizumab patients compared to placebo patients ($p < 0.0001$ for both vedolizumab treatment groups compared to placebo). Both vedolizumab dosing regimen treatment groups independently were significantly better than placebo. For patients who received 300 mg vedolizumab Q8W, the difference from placebo was 26.1% (95% CI: 14.9, 37.2) and in the Q4W dosing group (300 mg vedolizumab dosed Q4W), the difference from placebo was 29.1% (95% CI: 17.9, 40.4). For both dosing regimens, the relative risks were of similar magnitude and favored vedolizumab (2.7 for Q8W, 2.8 for Q4W).

3.1.2 Exposure-Response for Effectiveness

Sponsor conducted an exposure-efficacy analysis utilizing data from Study C13006 to evaluate the adequacy of the proposed dose regimen for induction and maintenance in UC patients. Vedolizumab concentrations were grouped in quartiles, and the associated clinical remission and clinical response were calculated. In UC patients, for both induction and maintenance, there was a concentration-response, where higher concentrations were associated with higher efficacy. In induction, concentrations below 17 $\mu\text{g/mL}$ had a clinical remission similar to placebo. In maintenance, concentrations above 9 $\mu\text{g/mL}$ were associated with higher efficacy (Table 4 and Table 5).

Table 4. Vedolizumab Response (Clinical Remission) by Concentration Quartiles at Induction (Week 6; C13006, Intent-to-Treat Population)

	Placebo	Vedolizumab Concentration Quartiles			
		Q1	Q2	Q3	Q4
Vedolizumab Conc ($\mu\text{g/mL}$)		≤ 16.7	$> 16.7\text{-}24.8$	$> 24.8\text{-}33.3$	$> 33.3\text{-}65.6$
N	133	54	53	55	54
Clinical Remission % (CI)	6.0% (2.0; 10.1)	5.6% (1.2; 15.4)	11.3% (2.8; 19.9)	16.4% (6.6; 26.1)	37.0% (24.2; 49.9)

(Source: Sponsor's Summary of Clinical Pharmacology, Table 3-13)

Table 5. Vedolizumab Response (Clinical Remission) by Concentration Quartiles at Maintenance (Week 46; C13006, ITT Population)

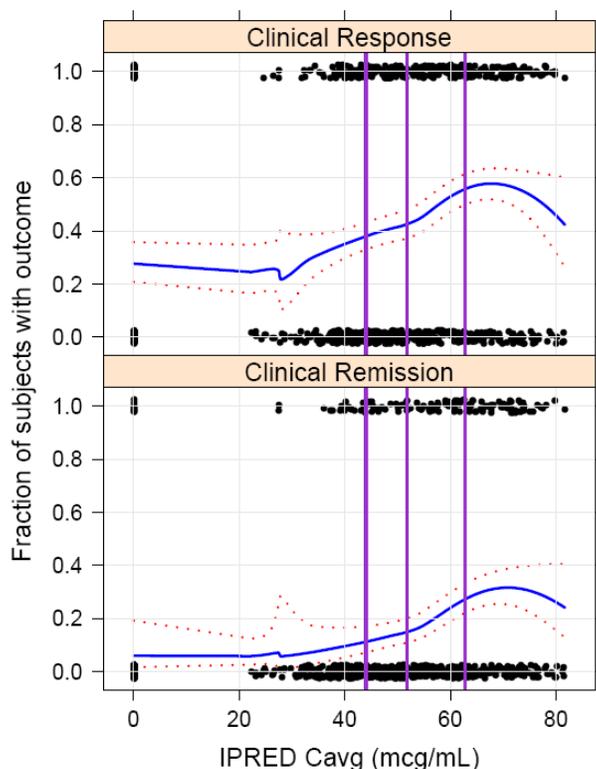
	Placebo	Vedolizumab Concentration Quartiles			
		Q1	Q2	Q3	Q4
Vedolizumab Conc (µg/mL)		≤ 9.2	> 9.2-18.6	> 18.6-40.0	> 40.0 -101.0
N	32	39	39	40	40
Clinical Remission % (CI)	31.3% (15.2; 47.3)	53.8% (38.2; 69.5)	64.1% (49.0; 79.2)	65.0% (50.2; 79.8)	80.0% (67.6; 92.4)

(Source: Sponsor’s Summary of Clinical Pharmacology, Table 3-14)

Sponsor also conducted analysis based on logistic regression modeling (using average predicted concentration as exposure) to investigate possible confounders of the exposure-response relationship. Exploratory exposure-response plots for both induction and maintenance are shown in **Figure 15** and **Figure 16**.

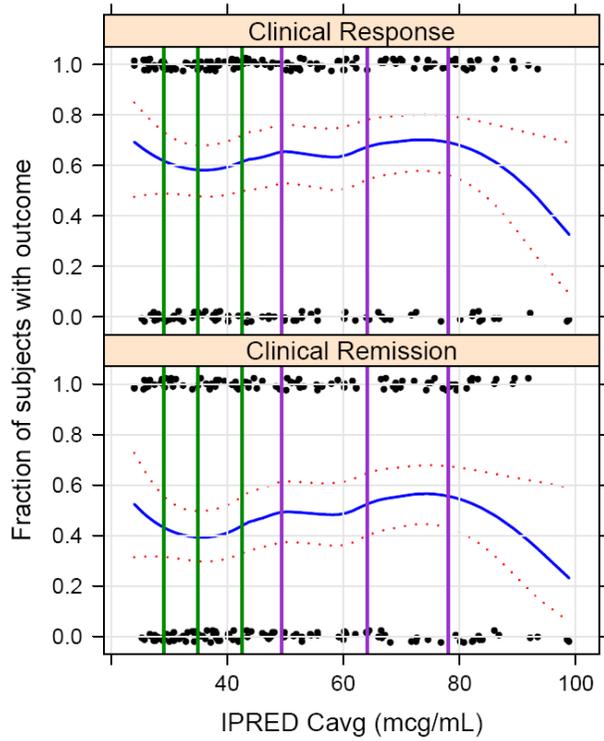
Exploratory exposure-response analysis demonstrated that increasing Coverage leads to higher probability of clinical remission and clinical response at Week 6. Adjusting for covariates that are related to both exposure (Coverage) and outcome yields an estimated exposure-response relationship that is positive but shallower than in the exploratory analysis, suggesting that this unadjusted model, and any exposure-response relationships derived from plots or tables of observed data alone, provide a positively biased estimate of the exposure-response relationship (Table 6 and Table 7).

Figure 15. Sponsor’s Exposure-Response plots for efficacy in patients with Ulcerative Colitis– Week 6



(Source: Sponsor’s Exploratory Analysis of Confounders for Exposure-Response Report, Figure 8)

Figure 16. Sponsor’s Exposure-Response plots for efficacy in patients with Ulcerative Colitis– Week 52



(Source: Sponsor’s Exploratory Analysis of Confounders for Exposure-Response Report, Figure 9)

Table 6. Parameter estimates (standard errors) from base, covariate, and interaction models for clinical remission, Ulcerative Colitis population, Study 13006

	<i>Dependent variable:</i>		
	Clinical Remission		
	Base model	Adjusted model	Interaction model
Placebo	5.181*** (1.459)	4.231*** (1.525)	4.027*** (1.551)
log(Coverage+1)	1.624*** (0.347)	1.381*** (0.365)	1.476*** (0.384)
Baseline ALB - 35		0.020 (0.020)	0.161 (0.099)
log(baseline FeCP) - 6.5		-0.086 (0.068)	0.232 (0.244)
prior anti-TNFa		-0.446** (0.203)	-0.998 (0.852)
log(Coverage+1)*(Baseline ALB-35)			-0.036 (0.025)
log(Coverage+1)*(log(baseline FeCP)-6.5)			-0.084 (0.062)
log(Coverage+1)*(prior anti-TNFa)			0.144 (0.216)
Intercept	-7.962*** (1.413)	-6.883*** (1.479)	-7.244*** (1.550)
Observations	845	845	845
Log likelihood	-366.844	-362.579	-360.408
Akaike Inf. Crit.	739.687	737.159	738.817

Note:

*p<0.1; **p<0.05; *** p<0.01

ALB = albumin (g/L); Coverage = average concentration since first dose calculated as UCcumulative/TAFD (mcg/mL); FeCP = fecal alproctectin (mg/kg); prior anti-TNFa = 0 (naive) and 1 (failed)

(Source: Sponsor's Exploratory Analysis of Confounders for Exposure-Response Report, Table 3)

Table 7. Parameter estimates (standard errors) from base, covariate, and interaction models for clinical response, Ulcerative Colitis population, Study 13006

	<i>Dependent variable:</i>		
	Clinical Response		
	Base model	Adjusted model	Interaction model
Placebo	4.565*** (1.136)	3.814*** (1.191)	3.813*** (1.194)
log(Coverage+1)	1.358*** (0.280)	1.169*** (0.294)	1.171*** (0.301)
Baseline ALB - 35		0.008 (0.015)	0.018 (0.042)
log(baseline FeCP) - 6.5		-0.034 (0.053)	0.009 (0.135)
prior anti-TNFa		-0.492*** (0.148)	-0.591 (0.397)
log(Coverage+1)*(Baseline ALB-35)			-0.003 (0.011)
log(Coverage+1)*(log(baseline FeCP)-6.5)			-0.013 (0.036)
log(Coverage+1)*(prior anti-TNFa)			0.029 (0.107)
Intercept	-5.522*** (1.120)	-4.588*** (1.175)	-4.597*** (1.194)
Observations	845	845	845
Log likelihood	-558.164	-552.162	-552.043
Akaike Inf. Crit.	1,122.327	1,116.324	1,122.087

Note:

*p<0.1; **p<0.05; ***p<0.01

ALB = albumin (g/L); Coverage = average concentration since first dose calculated as UCcumulative/TAFD (mcg/mL); FeCP = fecal alprotectin (mg/kg); prior anti-TNFa = 0 (naive) and 1 (failed)

(Source: Sponsor's Exploratory Analysis of Confounders for Exposure-Response Report, Table 4)

Reviewer's Comments:

1. Sponsor's exposure-response analysis for confounding factors was different from the reviewer's in two ways. First, besides the ITT population, the sponsor also included patients from the open label arms (Cohort 2 for induction and Week 6 Non-responders in the Q4W arm for maintenance). Second, the sponsor used average concentration after first doses as exposure metrics while reviewer uses trough concentrations. Similar to sponsor's results, reviewers' analysis also identified significant exposure-response relationships in the

induction phase after accounting for known baseline confounding factors, but with a steeper slope of the relationship.

2. Sponsor's plots were somewhat misleading. The solid lines were local regression smooth (loess) lines spanning the observed data, which is not the correct way to visualize the logistic regression curve. The better approach is to use the model predicted line overlaying with observed data in quartiles.

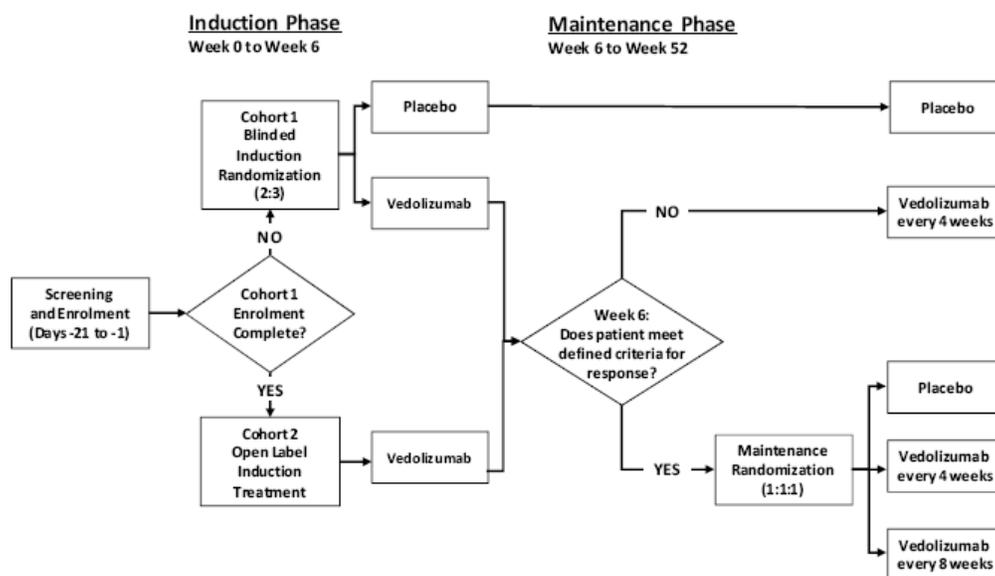
3.2 Crohn's Disease

3.2.1 Clinical Trials

Trial c13007:

Trial c13007 was a phase 3, randomized, placebo-controlled, blinded, multicenter study of the induction and maintenance of clinical response and remission by vedolizumab in patients with moderate to severe crohn's disease. The trial design is shown in Figure 17.

Figure 17. Schematic of Trial c13007.



(Source: Sponsor's Clinical Study Report for Trial c13007)

The 6-week Induction Phase contained 2 cohorts of patients. Eligible patients enrolled in Cohort 1 were to be randomized in a 3:2 ratio to double-blind vedolizumab 300 mg or placebo administered intravenously. The second cohort of patients were enrolled into the Induction Phase to provide sufficient numbers of patients to fully power the Maintenance Study efficacy analyses. All patients in Cohort 2 were to receive open-label vedolizumab, administered at a dose of 300 mg at Weeks 0 and 2.

Efficacy was assessed at Week 6 for all patients. The Induction Study efficacy analyses were based on the assessments performed on patients included in the randomized, double-blind

treatment groups in Cohort 1. Safety analyses for the Induction Phase include all safety data collected from baseline through the Week 6 induction assessments.

The Maintenance Phase began after the Week 6 efficacy assessments and continued through Week 52. The maintenance treatment group assignment was based on both the Week 6 treatment response and the induction treatment assignment. At Week 6, vedolizumab-treated patients in both Cohorts 1 and 2 who had achieved clinical response (as defined by the protocol and assessed by the investigator) were to be randomized in a 1:1:1 ratio to one of the following blinded maintenance regimens: vedolizumab 300 mg Q4W, vedolizumab 300 mg Q8W, or placebo. These patients comprised the Maintenance ITT population, the primary efficacy population.

Patients in Induction Phase Cohorts 1 and 2 who had received vedolizumab induction treatment and had not achieved clinical response at Week 6 were to be assigned to receive open-label vedolizumab Q4W from Week 6 through Week 52. These patients contribute to the non-ITT population of the Maintenance Phase.

Patients in Induction Phase Cohort 1 who had been randomized to placebo were assigned to continue receiving placebo from Week 6 through Week 52. These patients also contribute to the non-ITT population of the Maintenance Phase.

The primary efficacy assessments for induction were the differences in the proportions of patients with clinical remission at Week 6 and enhanced clinical response at Week 6 in the vedolizumab group versus the placebo group. Clinical remission was defined as CDAI score \leq 150 points and enhanced clinical response was defined as a $>$ 100-point decrease in CDAI score from baseline. The primary efficacy assessment for maintenance was the difference in the proportions of patients with clinical remission at Week 52 in the vedolizumab Q4W versus placebo groups and vedolizumab Q8W versus placebo groups, defined as CDAI score $<$ 150 points.

A statistically significant greater proportion of vedolizumab-treated patients (14.5%) achieved clinical remission at Week 6 compared with patients who received placebo (6.8%). The treatment difference from placebo was 7.8% (95% CI 1.2, 14.3; $p = 0.0206$), with a relative risk of 2.1 in favor of vedolizumab. Although a trend in favor of vedolizumab was observed for enhanced clinical response at Week 6, the difference between the vedolizumab and placebo groups was not statistically significant. The treatment difference from placebo was 5.7% (95% CI -3.6, 15.0; $p = 0.2322$), with a relative probability of achieving enhanced clinical response at Week 6 of 1.2.

The pre-specified Hochberg method was applied to control the overall Type I error rate at a 5% significance level for the multiple comparisons of the primary endpoints. Since the p-value for the endpoint of enhanced clinical response at Week 6 was $>$ 0.05, the p-value for the endpoint of clinical remission at Week 6 was tested at the 0.025 level of significance. As the p-value for clinical remission at Week 6 was $<$ 0.025 ($p = 0.0206$), the study is considered to have met the primary endpoint of clinical remission at Week 6.

Statistically significantly greater proportions of vedolizumab-treated patients in the Q8W (39.0%) and Q4W (36.4%) treatment groups achieved clinical remission at Week 52 compared with patients who received placebo (21.6%; $p = 0.0007$ and $p = 0.0042$, respectively).

Results of the exposure-response analyses for effectiveness are shown in Section 3.2.2.

Trial c13011

This was a phase 3, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vedolizumab for the induction of clinical response and remission in patients with moderately to severely active CD. Of the total patients enrolled, 75% were to have previously failed TNF α antagonist therapy and 25% were to have been naïve to TNF α antagonist therapy. Patients were randomized 1:1 to receive either vedolizumab or placebo at Weeks 0, 2, and 6. The randomization to treatment assignment was stratified by the presence or absence of each of the following: 1) previous failure of TNF α antagonist therapy or naïve to TNF α antagonist therapy, 2) concomitant use of oral corticosteroids, and 3) concomitant use of immunomodulators (6-mercaptopurine [6-MP], azathioprine, or methotrexate).

Final enrollment was 416 patients from 107 sites in 19 countries, each of whom received study drug. Among the 416 patients, 315 (76%) had previously failed TNF α antagonist therapy and 101 (24%) were naïve to TNF α antagonist therapy.

Patients were male or female, must have been between 18 and 80 years of age, and must have had moderately or severely active CD (defined as a Crohn's Disease Activity Index [CDAI] score of 220 to 400 points). Patients must have demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of immunomodulators and/or TNF α antagonists. Patients outside of the US may have also been enrolled on the basis of prior corticosteroid treatment failure.

For the analysis of the primary endpoint (clinical remission at week 6), no statistically significant difference was observed between the vedolizumab (15.2%) and placebo (12.1%) groups for the proportions of patients in clinical remission at Week 6 in the TNF α Antagonist Failure ITT Subpopulation. The treatment difference from placebo was 3.0% (95% CI -4.5, 10.5; $p = 0.4332$), with a relative probability of achieving clinical remission at Week 6 of 1.2 (relative risk with 95% CI 0.7, 2.2).

3.2.2 Exposure-Response for Effectiveness

Exposure-response analyses for efficacy (clinical remission and enhanced clinical response) were conducted by the sponsor using data primarily from trial c13007. The sponsor reported two separate exposure response analyses. In their summary of clinical pharmacology clinical remission rates were reported for each concentration quartile at week 6 for both trials c13007 and c13011 and for week 52 in trial c13007 (Table 8, Table 9, and Table 10). Whereas the sponsor also evaluated both univariate and multivariate logistic regression models for the probability of clinical response, enhanced clinical response, and/or clinical remission (Figure 18, Figure 19, and Table 11) using data from trial c13007 as part of an analysis of potential confounding factors.

Table 8. Vedolizumab Response (Clinical Remission) by Concentration Quartiles at Induction (Week 6, Study c13007).

	Placebo	Vedolizumab Concentration Quartiles			
		Q1	Q2	Q3	Q4
Vedolizumab Conc (µg/mL)		≤ 15.2	> 15.2-24.0	> 24.0-33.8	> 33.8-142.0
N	135	49	51	50	50
Clinical Remission % (CI)	7.4% (3.0; 11.8)	6.1% (1.3; 16.9)	18.0% (7.4, 28.6)	14.0% (4.4; 23.6)	22.0% (10.5; 33.5)

(Source: Sponsor's Summary of Clinical Pharmacology, Table 3-15)

Table 9. Vedolizumab Response (Clinical Remission) by Concentration Quartiles at Maintenance (Week 46, Study c13007).

	Placebo	Vedolizumab Concentration Quartiles			
		Q1	Q2	Q3	Q4
Vedolizumab Conc (µg/mL)		≤ 10.0	> 10.0-18.6	> 18.6-32.6	> 32.6-70.8
N	43	39	39	39	40
Clinical Remission % (CI)	51.2% (36.2; 66.1)	74.4% (60.7; 88.1)	74.4% (60.7; 88.1)	66.7% (51.9; 81.5)	75.0% (61.6; 88.4)

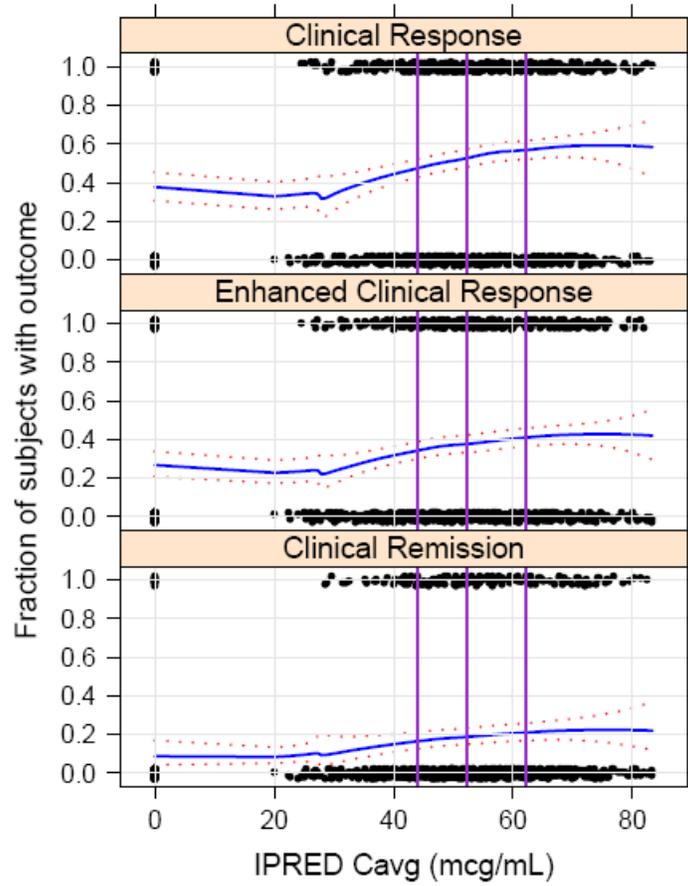
(Source: Sponsor's Summary of Clinical Pharmacology, Table 3-16)

Table 10. Vedolizumab Response (Clinical Remission) by Concentration Quartiles at Induction (Week 6, Study c13011).

	Placebo	Vedolizumab Concentration Quartiles			
		Q1	Q2	Q3	Q4
Vedolizumab Conc (µg/mL)		≤ 17.1	> 17.1-24.7	> 24.7-32.5	> 32.5-128
N	190	49	50	47	52
Clinical Remission % (CI)	12.1 (7.5;16.7)	20.4 (9.1; 31.7)	18.0 (7.4; 28.6)	17.0 (6.3; 27.8)	25.0 (13.2; 36.80)

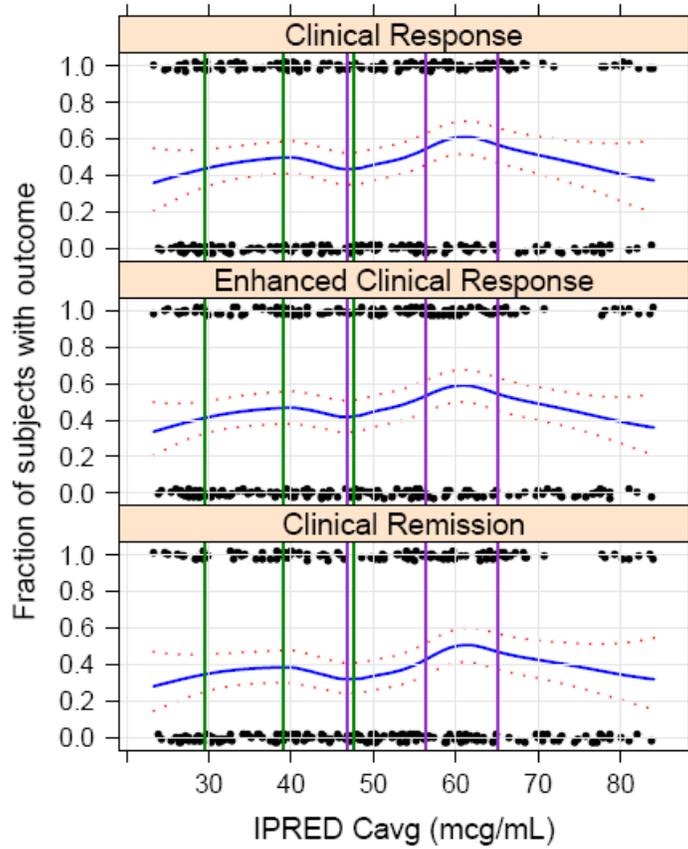
(Source: Sponsor's Summary of Clinical Pharmacology, Table 3-17)

Figure 18. Sponsor's Exposure-Response Analysis for efficacy in patients with Crohn's Disease – Week 6



(Source: Sponsor's Exploratory Analysis of Confounders for Exposure-Response Report, Figure 1)

Figure 19. Sponsor’s exposure response analysis for efficacy in patients with Crohn’s Disease – Week 52



(Source: Sponsor’s Exploratory Analysis of Confounders for Exposure-Response Report, Figure 5)

Table 11. Parameter estimates (standard errors) from base, covariate, and interaction models for clinical remission, Crohn’s Disease population, Study 13007.

	<i>Dependent variable:</i>		
	Clinical Remission		
	Base model	Adjusted model	Interaction model
Placebo	2.390* (1.242)	1.169 (1.340)	1.035 (1.372)
log(Coverage+1)	0.871*** (0.297)	0.585* (0.322)	0.596* (0.337)
Baseline ALB - 35		0.019 (0.018)	-0.044 (0.066)
log(baseline FeCP) - 6.5		0.111 (0.074)	-0.186 (0.287)
log(baseline CRP) - 2.5		-0.198*** (0.076)	-0.670** (0.302)
prior anti-TNFa		-0.614*** (0.172)	-1.140 (0.759)
log(Coverage+1)*(Baseline ALB-35)			0.017 (0.017)
log(Coverage+1)*(log(baseline FeCP)-6.5)			0.078 (0.073)
log(Coverage+1)*(log(baseline CRP)-2.5)			0.124 (0.077)
log(Coverage+1)*(prior anti-TNFa)			0.136 (0.193)
Intercept	-4.923*** (1.198)	-3.506*** (1.299)	-3.540*** (1.353)
Observations	994	994	994
Log likelihood	-449.973	-437.619	-434.885
Akaike Inf. Crit.	905.947	889.239	891.770

Note: *p<0.1; **p<0.05; ***p<0.01

(Source: Sponsor’s Exploratory Analysis of Confounders for Exposure-Response Report, Table 1)

Reviewer’s Comments:

There are two key points that differentiate the sponsor’s analysis with the reviewer’s analysis. The sponsor’s analysis 1) included ‘placebo’ subjects in their regression analysis and 2) utilized popPK average concentrations as the exposure metric. Regardless of the significance of the analysis, the shallow slope of the exposure-response suggests the dose is acceptable.

3.3 Population Pharmacokinetics of Vedolizumab in both UC and Crohn’s Disease

The population PK-PD dataset was developed from pooled data across study protocols C13002, C13006, C13007, C13009, and C13011. The vedolizumab population PK-PD dataset was comprised of 2554 subjects contributing a total of 18,427 evaluable vedolizumab serum concentrations.

Population PK-PD analyses for repeated-measures endpoints were conducted via nonlinear mixed effects modeling with the nonlinear mixed effects modeling (NONMEM) software, Version 7.2 (ICON Development Solutions, Hanover, MD). The first-order conditional estimation with $\eta - \varepsilon$ interaction (FOCEI) method was used for all model runs during the development of the population PK base model using extensive sampled data from studies C13002 and C13009. Results from the base model were subsequently used as prior information to selectively inform a subset of population PK model parameters in the full covariate model which was fit to sparse phase 3 data (C13006, C13007, C13011). The full covariate model was fit to the data using the full Bayesian Markov Chain Monte Carlo (MCMC) method in NONMEM.

Vedolizumab PK was described by a two-compartment model with parallel linear and nonlinear elimination. The model was parameterized in terms of clearance of linear elimination pathway (CLL), maximum elimination rate (V_{max}), concentration at half-maximum elimination rate (K_m), central volume of distribution (V_c), peripheral volume of distribution (V_p), and intercompartmental clearance (Q). The predefined covariates for the analysis included body weight as a predictor of clearance- and volume-related parameters; albumin, fecal calprotectin, Crohn's Disease Activity Index (CDAI), partial Mayo score, age, prior anti-tumor necrosis factor alpha (TNF α) treatment, inflammatory bowel disease (IBD) diagnosis type, subject-level human anti-human antibodies (HAHA) status, and adjuvant therapy (i.e., methotrexate, azathioprine, mercaptopurine, and aminosalicylates) as predictors of CLL ; and IBD diagnosis type as a predictor of V_c .

Allometric relationships using body weight were incorporated for the structural PK parameters CLL , V_{max} , V_c , V_p , and Q to describe the effects of body weight on vedolizumab PK. Differences between UC and CD subjects with respect to CLL and V_c were also investigated, but the results indicated that both PK parameters were the same in the two IBD diseases.

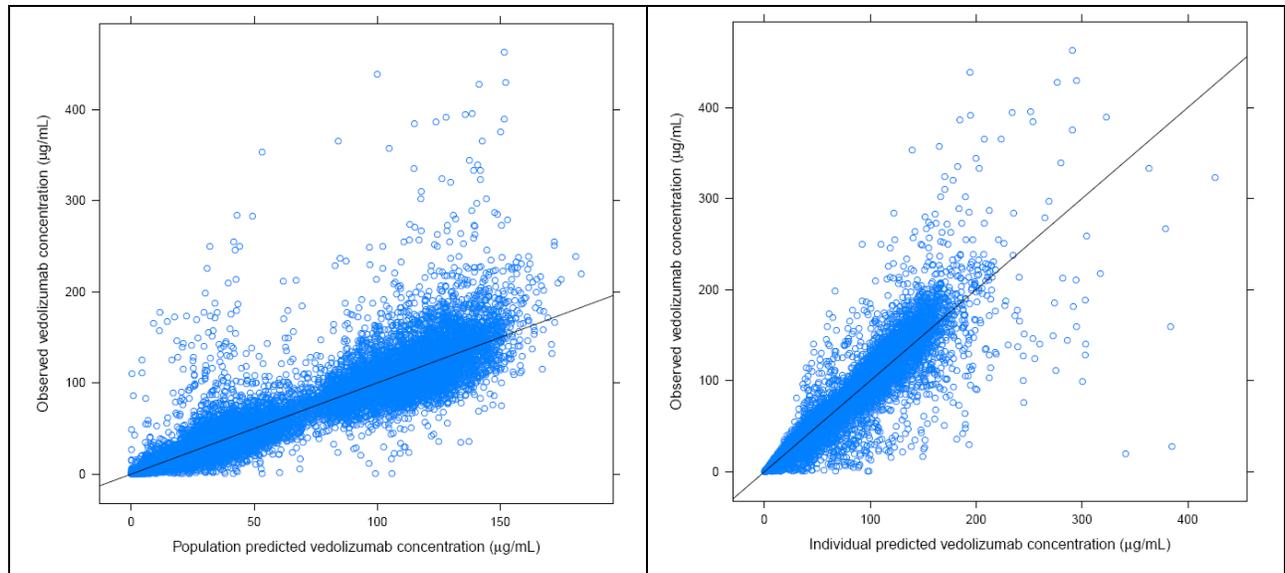
Parameter estimates for the final model are shown in Figure 20 and diagnostic/goodness of fit plots are shown in Figure 21.

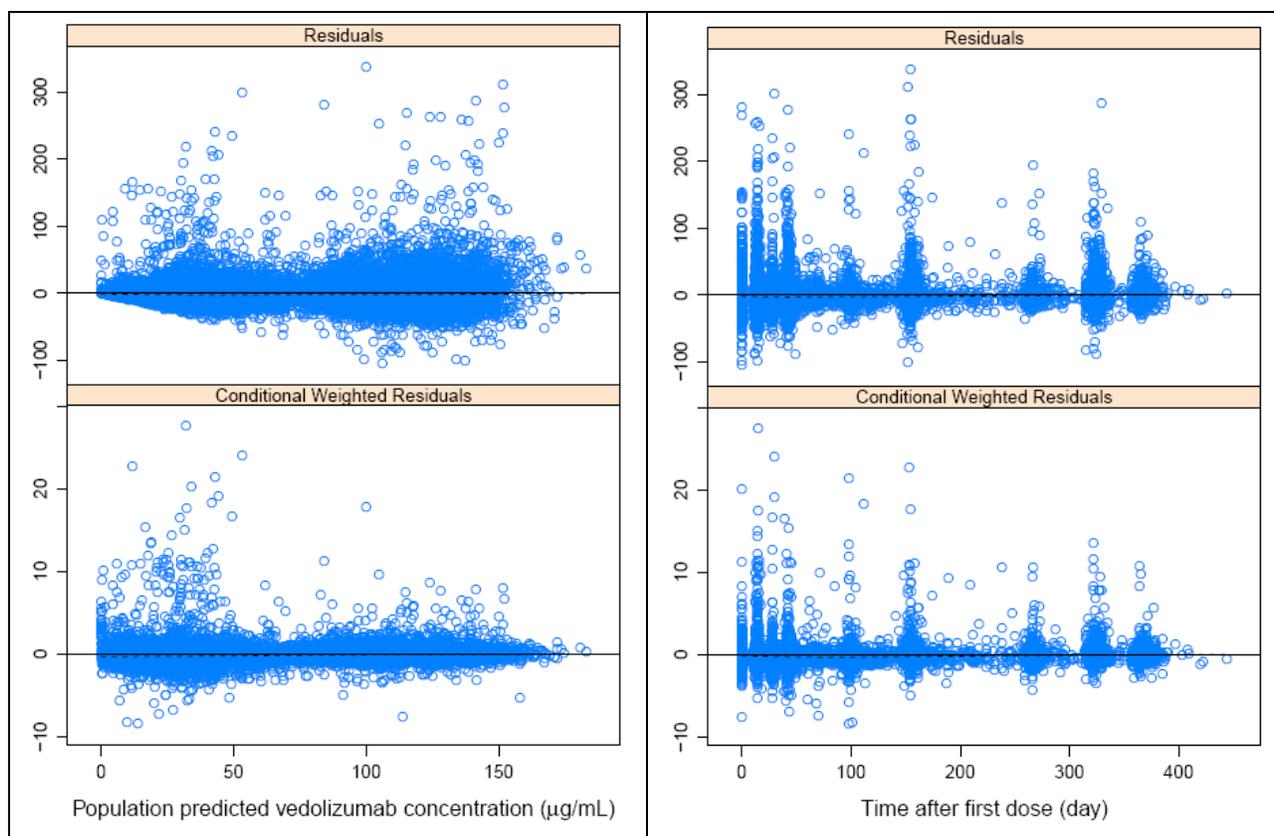
Figure 20. Parameter estimates for the final vedolizumab population PK model.

Parameter	Estimate*	Bayesian 95% CDI*
UC CL_L ($\exp(\theta_1)$)	0.159 L/day	(0.152, 0.166)
CD CL_L ($\exp(\theta_2)$)	0.155 L/day	(0.149, 0.161)
V_c ($\exp(\theta_3)$)	3.19 L	(3.14, 3.25)
V_p ($\exp(\theta_4)$)	1.66 L	(1.6, 1.72)
V_{max} ($\exp(\theta_5)$)	0.274 mg/day	(0.226, 0.329)
Q ($\exp(\theta_6)$)	0.119 L/day	(0.112, 0.127)
K_m ($\exp(\theta_7)$)	0.974 $\mu\text{g/mL}$	(0.715, 1.3)
$\Omega_{1,1} CL_L$	0.12 (%CV=34.6)	(0.111, 0.13)
$\Omega_{2,1} COV_{CL_L-V_c}$	0.0375	(0.0329, 0.0424)
$\Omega_{2,2} V_c$	0.0367 (%CV=19.2)	(0.0332, 0.0404)
$\Omega_{3,1} COV_{CL_L-V_{max}}$	-0.0699	(-0.111, -0.0327)
$\Omega_{3,2} COV_{V_c-V_{max}}$	-0.0536	(-0.0774, -0.0303)
$\Omega_{3,3} V_{max}$	1.11 (%CV=105)	(0.892, 1.37)
$\Omega_{4,4} V_p$	0 Fixed	(0, 0)
$\Omega_{5,5} Q$	0 Fixed	(0, 0)
$\Omega_{6,6} K_m$	0 Fixed	(0, 0)
σ_{prop}^2	0.0554 (%CV=23.5)	(0.054, 0.0569)

(Source: Sponsor's Population PK-PD Report, Table 7)

Figure 21. Diagnostic/Goodness-of-fit plots for the final vedolizumab population PK model.





(Source: Sponsor's Population PK-PD Report, Figures 18 - 21)

The sponsor concluded:

The effects of fecal calprotectin, CDAI score, partial Mayo score, age, prior anti-TNF α therapy, subject-level HABA status, and adjuvant therapy (azathioprine, methotrexate, mercaptopurine, and aminosaliclates) on *CLL* were generally well-defined and contained the null value, indicating that the results were not clinically meaningful based on covariate effect sizes of less than $\pm 25\%$ from the typical population value when evaluated over a representative range of covariate values. Inferences made with regards to the effect of HABA and adjuvant therapies, however, need to be made with caution given limitations of the data for these covariates. Due to the presence of drug interference with the HABA bioanalytical assay and inadequately populated start- and end-date domains in the adjuvant therapy source data, it was not possible to evaluate the time dependent effects of these covariates.

To evaluate the potential effect of adjuvant therapy (azathioprine, methotrexate, mercaptopurine, and aminosaliclates) on vedolizumab PK, the sponsor conducted an analyses for each drug or drug-class for only those individuals who were on the concomitant medication throughout the full duration of the trial independently from those who had an unknown duration of medication during the trial. The results are discussed further in detail of Section 2.4.2.

Reviewer's Comments:

The sponsor's population PK analysis appears appropriate for evaluating the effects of potential covariates on vedolizumab PK.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor's exposure response analysis suggests there is an exposure response relationship for the primary endpoints studied in patients with UC and CD. Additionally, this relationship suggests that a higher dose may lead to better efficacy results. However, the two randomized maintenance arms at Q4 weeks and Q8 weeks show no difference in effectiveness. This review aims to clarify if the proposed dosing regimen is appropriate for the induction and maintenance of remission in patients with UC or CD.

4.2 Objectives

Analysis objectives are:

1. Evaluate exposure response relationships for potential confounding factors
2. Evaluate Phase 2 data for evidence of exposure-response for effectiveness
3. Review the sponsor's labeling statements regarding:
 - Dose titration to Q4 weeks (b) (4)
 - Discontinuation of therapy after Week 14 if lack or decrease of response (b) (4)
 - Population PK assessments including DDI and PK values (Proposed label - Sections 7.1 and 12.3).

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
c13006	effpat.xpt	\\cdsesub1\bla\CTD_Submissions\STN125476\0002\m5\datasets\c13006\analysis\legacy\datasets\
c13006	pc.xpt	\\cdsesub1\bla\CTD_Submissions\STN125476\0002\m5\datasets\c13006\tabulations\sdtm\
c13007	effpat.xpt	\\cdsesub1\bla\CTD_Submissions\STN125476\0002\m5\datasets\c13007\analysis\legacy\datasets\
c13007	pc.xpt	\\cdsesub1\bla\CTD_Submissions\STN125476\0002\m5\datasets\c13007\tabulations\sdtm
c13011	effpat.xpt	\\cdsesub1\bla\CTD_Submissions\STN125476\0002\m5\datasets\c13011\analysis\legacy\datasets\
c13011	pc.xpt	\\cdsesub1\bla\CTD_Submissions\STN125476\0002\m5\datasets\c13011\tabulations\sdtm\

4.3.2 Software

The following software packages were used in the analyses.

- SAS (SAS Institute Inc., Cary, NC)
- NONMEM (Icon, Ellicott City, MD)

4.3.3 Models

Pharmacokinetic simulations were performed using the sponsor's population PK model (see sponsor's analysis section) to evaluate the feasibility of increasing the number of doses during the induction of UC remission. The post hoc estimates for 100 subjects from the population PK model were used to simulate vedolizumab concentration time profiles over a period of 14 weeks with 100 replications.

Ulcerative Colitis Exposure-Response Analysis:

For induction phase, the exposure response relationship was modeled between probability of achieving clinical response/remission at Week 6 and Week 6 vedolizumab trough concentrations using logistic regression. Similarly, the relationship between probability of achieving clinical response at Week 14 and Week 14 vedolizumab trough concentrations was assessed.

Clinical response is defined as reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ decrease from baseline, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.

Clinical remission is defined as a Mayo score ≤ 2 points and no individual subscore > 1 . The Mayo score is a composite score of UC disease activity ranging from 0 to 12 based on the sum of 4 subscores: endoscopy (0-3), stool frequency (0-3), rectal bleeding (0-3), and physician's global assessment (0-3).

Numerous risk factors (such as age, gender, baseline Mayo score, baseline fecal calprotectin, albumin level, prior immunomodulator use and previous exposure to anti-TNF therapy, etc.) were each tested in a univariate logistic regression model versus Week 6 clinical response/remission. Statistically significant risk factors were incorporated in a multivariate logistic regression model to determine Week 6 vedolizumab trough concentrations were still significant after correction for these factors.

A Kaplan-Meier plot displayed the proportion of subjects who have not experienced treatment failure versus time for the four quartiles of Week 6 vedolizumab trough concentrations and placebo. Treatment Failure is defined as disease worsening, need for rescue medications or surgical intervention for treatment of UC, or study drug-related adverse event leading to discontinuation from the study. The time to treatment failure was expressed in days after the initial dose. Patients were censored if they dropped out or did not experience treatment failure until end of the study.

Crohn's Disease Exposure Response Analysis:

Logistic regressions were conducted for the probability of clinical remission or enhanced clinical response in studies c13007 and c13011, where mean trough concentration was the only independent variable in the model. This was performed to ascertain an approximate extent of impact this potential factor may have on clinical remission and enhanced clinical response. Results are shown in Figure 8 and Figure 11.

Multivariate logistic regression models were developed to further evaluate the effects of mean trough concentration in the presence of other possible confounding factors. Potential covariates tested included: mean trough concentration, sex, age, race, prior disease duration, region of GI tract where disease is located, concomitant corticosteroid use, prior failure/naive to TNF, inadequate response to prior TNF treatment, baseline CDAI score, baseline EI manifestations

score, baseline HBI, baseline C-reactive protein, calprotectin, concomitant immunomodulator use. The “proc logistic” routine in SAS was implemented with an automated forward selection and backward elimination (alpha = 0.05, entry criteria = 0.1 and elimination criteria = 0.05).

See Section 4.4 for further details.

4.4 Results

4.4.1 Ulcerative Colitis

The potential relationship between the primary endpoints and the corresponding trough vedolizumab concentrations was assessed using logistic regression analysis. The primary efficacy endpoints are the clinical response at Week 6 (induction endpoint) and clinical remission at Week 52 (maintenance endpoint).

The effect of increasing induction phase dosing frequency was determined by simulating the two dosing regimens at a population mean level using the sponsor’s population PK model.

4.4.1.1 Exposure-Response Analysis at Week 6

Exposure-Response Analysis using univariate logistic regression modeling showed statistically-significant relationships ($p < 0.0001$) between clinical response or remission at Week 6 and Week 6 vedolizumab trough concentration (Figure 1). Univariate logistic regression was also performed on risk factors (such as age, gender, baseline Mayo score, baseline fecal calprotectin, albumin level, prior immunomodulator use and previous exposure to anti-TNF therapy, etc.) to determine if they are associated with efficacy status. Significant predictors of Week 6 response and remission are shown in **Table 13** and **Table 14**, respectively.

Table 13. Significant predictors of Clinical Response at Week 6 from Univariate Analysis of Study C13006 with corresponding Parameter Estimates.

Variable	Odds Ratio	Lower 95%	Upper 95%	Pr
	Estimate	Confidence Limit	Confidence Limit	> Chi-Square
Week 6 Vedolizumab Concentration	1.042	1.027	1.058	<.0001
Albumin	1.168	1.101	1.24	<.0001
Baseline Mayo Sore	0.799	0.701	0.911	0.0008
Previous Exposure to TNF α antagonist	0.589	0.379	0.916	0.0188
Prior TNF α antagonist Failure	0.581	0.369	0.915	0.0192
Baseline Concomitant Immunomodulator Use	1.651	1.041	2.617	0.033

Table 14. Significant predictors of Clinical Remission at Week 6 from Univariate Analysis of Study C13006 with corresponding Parameter Estimates.

Variable	Odds Ratio	Lower 95%	Upper 95%	Pr
	Estimate	Confidence Limit	Confidence Limit	> Chi-Square
Week 6 Vedolizumab Concentration	1.046	1.026	1.066	<.0001
Albumin	1.172	1.074	1.279	0.0004

Baseline Mayo Sore	0.626	0.51	0.769	<.0001
Previous Exposure to TNF α antagonist	0.339	0.166	0.693	0.003
Prior TNF α antagonist Failure	0.402	0.192	0.84	0.0154
Baseline Concomitant Immunomodulator Use	2.384	1.269	4.478	0.0069

For patients with prior exposure or failure to anti-TNF α therapy, the model predicts that their chances to achieve Week 6 clinical response and remission are lower than the patients without prior exposure or failure. This is consistent with what is clinically expected and was observed in the clinical trials. However, for patients who were on baseline concomitant immunomodulator therapy, the model predicts that their chances to achieve Week 6 response or remission are higher. The model also predicts that the probability of Week 6 response and remission would be higher with decreasing baseline Mayo score, and increasing albumin level.

In order to adjust for the confounding factors and determine if concentrations is the driver for Week 6 clinical response or remission, multivariate logistic regression was performed. The multivariate analyses selected significant factors based on a stepwise selection and backwards elimination. Baseline Mayo score is the only risk factor demonstrating statistically significant effects to both clinical response and remission at Week 6. Probability of achieving clinical response decreases with higher baseline mayo score and lower albumin level. Probability of achieving clinical remission decreases with higher baseline mayo score as well, and is higher in patients with concomitant immunomodulator use at baseline. After accounting for all other significant factors, Week 6 vedolizumab trough concentration was still found to be significantly associated with Week 6 clinical response or remission (**Table 15** and **Table 16**). In addition, we did sensitivity analysis to include TNF α as a predictor as well since clinically it is known to be an important baseline risk factor for response and remission. Even after including TNF α , the concentration was still significant. The overall findings of exposure-response relationships at Week 6 suggest that a higher induction dose may lead to improved response/remission rate at Week 6.

Table 15. Significant predictors of Clinical Response at Week 6 from Multivariate Analysis of Study C13006 with corresponding Parameter Estimates.

Variable	Odds Ratio Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Pr > Chi-Square
Week 6 Vedolizumab Concentration	1.037	1.021	1.053	<.0001
Baseline Mayo Sore	0.838	0.728	0.964	0.0135
Albumin	1.124	1.055	1.197	0.0003

Table 16. Significant predictors of Clinical Remission at Week 6 from Multivariate Analysis of Study C13006 with corresponding Parameter Estimates.

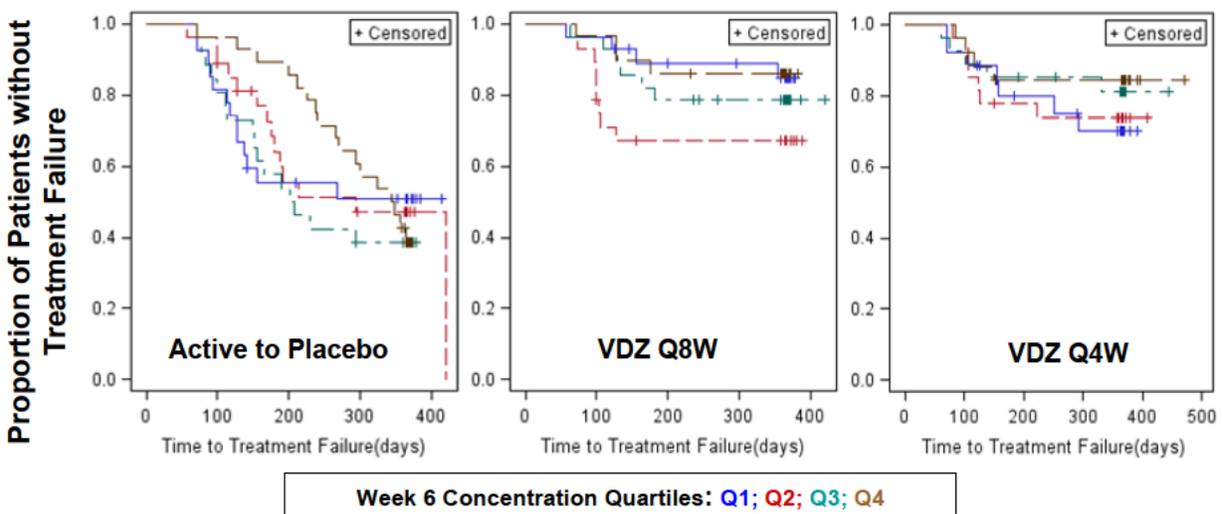
Variable	Odds Ratio Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Pr > Chi-Square
Week 6 Vedolizumab Concentration	1.041	1.021	1.062	0.0005
Baseline Mayo Sore	0.64	0.519	0.79	<.0001

Baseline Concomitant Immunomodulator Use	2.455	1.232	4.891	0.024
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Exposure response relationship was further explored between Week 6 concentrations and time to treatment failure using Kaplan Meier analysis to examine if patients with higher Week 6 concentrations were associated with longer time to treatment failure.

Kaplan-Meier plots were generated to track the proportion of patients that who have not experienced treatment failure over time since first dose. The patients in each maintenance phase dosing group were grouped into four quartiles of Week 6 vedolizumab trough concentration and a placebo group (**Figure 22**). The plots suggest that there was no effect of Week 6 concentrations on time to treatment failure. It is important to note that even though we are relating Week 6 concentrations to treatment failure, the time to treatment failure will also be influenced by concentrations observed in the maintenance doses. Nevertheless, there was no relationship evident between Week 6 vedolizumab concentration and time to treatment failure.

Figure 22. No significant exposure-response relationship for time to treatment failure. Kaplan-Meier plot of the proportion of patients who have not experienced treatment failure vs. vedolizumab Week 6 trough concentration quartile (Study C13006)



Pharmacokinetic Simulations for Alternative Dosing Regimens

Simulated concentration profiles demonstrated that increasing induction phase dosing frequency would significantly increase vedolizumab concentration at Week 6 (**Figure 23**). Simulated mean trough concentration at Week 6 increases by ~2-fold with an additional 300 mg dose at Week 4, and ~2.5-fold with additional two doses at Week 1 and 4 (**Table 17**). Therefore, it is possible that exploring higher induction dose would provide additional benefit.

Figure 23. Simulated Vedolizumab Pharmacokinetic Profiles Comparing Three Induction Dosing Regimens (Proposed dose, Additional 300mg dose at Week 4, Additional 300mg doses at Week 1 and 4)

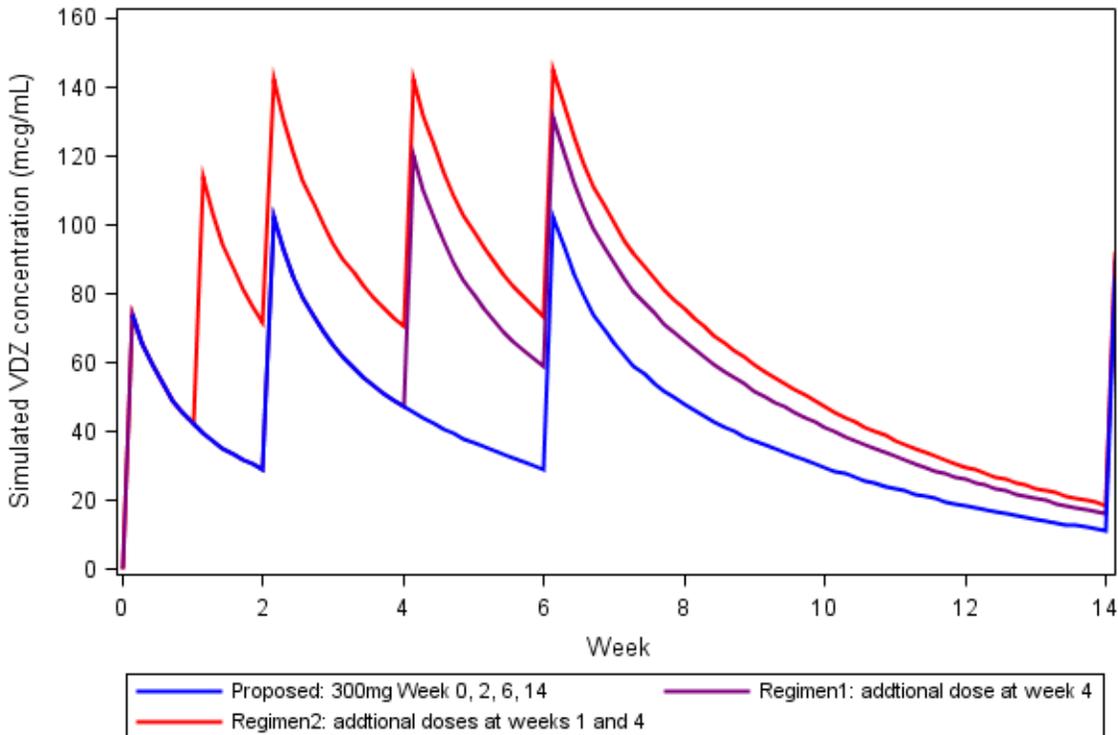


Table 17. Simulated Vedolizumab Trough Concentration Profiles Comparing Three Induction Dosing Regimens (Proposed dose, Additional 300mg dose at Week 4, Additional 300mg doses at Week 1 and 4)

Week	Simulated Vedolizumab Trough Concentration ($\mu\text{g/mL}$)		
	Proposed: 300mg Week 0, 2, 6, 14	Additional Week-4 dose	Additional Week-1 and Week-4 doses
1	42.27	42.27	42.27
2	29.24	29.24	71.83
4	47.30	47.30	70.35
6	29.11	58.85	73.49
14	11.41	16.21	18.67

So, along with a trend of increased Week 6 response rate with increasing concentrations, increasing the dose may result in more responders in the induction phase which may possibly result in more people in remission at Week 52. However, a delayed-response phenomenon was observed (highlighted in Section 1.1.1), indicating Week 6 may still be early for exploring the exposure-response relationship. Therefore, we agree with the sponsor proposed dosing regimen but recommend them to explore option of higher induction doses post-approval.

4.4.1.2 Exposure-Response Analysis at Week 52

The magnitude of clinical benefit were found similar between the Q8W and Q4W vedolizumab regimens based on dose-response results, as demonstrated by clinical primary endpoint (clinical remission at Week 52) and exploratory endpoints (see Section 1.1.2). Therefore no exposure-response analysis was needed.

4.4.1.3 Review the sponsor's labeling statements regarding:

- **Dose titration to Q4 weeks** (b) (4): Refer to Key question section 1.1.3
- **Discontinuation of therapy in patients who show no evidence of therapeutic benefit by Week 14** (b) (4): Refer to Key question section 1.1.4

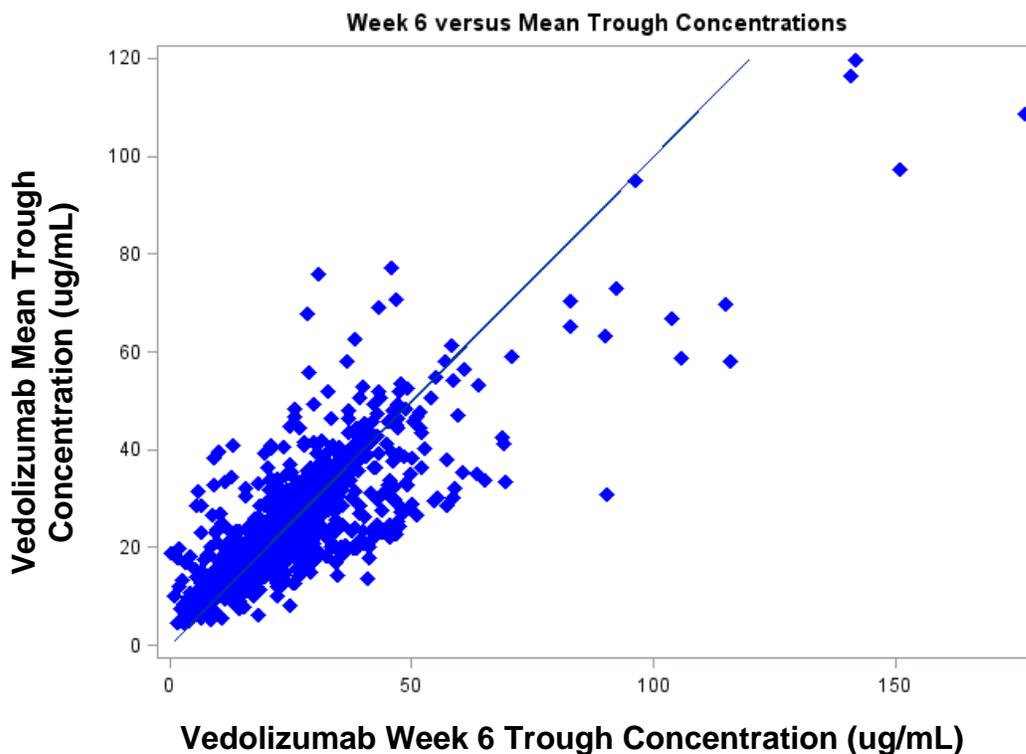
4.4.2 Crohn's Disease

4.4.2.1 Exposure-Response Analyses

Exposure Metric:

The exposure-metric used for all exposure-response analysis is the mean of all trough concentrations ("Pre-dose") for each individual within the study treatment period. The mean trough concentration was implemented to reduce residual error in the PK assessment. For consistency with the UC analysis, all exposure-response analyses were repeated with Week 6 trough concentrations and the conclusions were unchanged. This is likely due to the high degree of correlation between these two metrics (Figure 24).

Figure 24. Mean trough (pre-dose) concentrations are correlated with week 6 concentrations. Symbols represent observations for each individual. The solid line is the line of identity.



Logistic Regression Analysis for Clinical Remission and Enhanced Clinical Response:

Univariate Regression Analysis

Logistic regressions were conducted for the probability of clinical remission or enhanced clinical response in studies c13007 and c13011, where mean trough concentration was the only independent variable in the model. This was an initial assessment performed to ascertain the approximate extent of vedolizumab exposure on clinical remission and enhanced clinical response. Results are shown in Figure 8 and Figure 11. No consistent trend was observed between endpoints, between studies, and at across different study visits (weeks 6, 10, 14, and 52). In no case evaluated was the exposure-response relationship significant (e.g. lowest p-value was 0.15). These analyses should be considered in light of the fact that other factors present may also influence the clinical remission or enhanced clinical response rates (baseline CDAI score, prior TNF-treatment and/or failure). Thus, multivariate analyses were conducted to incorporate these potential confounders into the analysis.

Multivariate Regression Analysis:

Multivariate logistic regression models were developed to further evaluate the effects of mean trough concentration in the presence of other possible confounding factors. Potential covariates tested included: mean trough concentration, sex, age, race, prior disease duration (CDDUR), region of GI tract where disease is located (LOCALIZE), concomitant corticosteroid use (RDCSTER), prior failure/naive to TNF (RDTNF), inadequate response to prior TNF treatment

(INADTNF), baseline CDAI score (BASECDAI), baseline EI manifestations score (BASEEIS), baseline HBI (BASEHBI), baseline C-reactive protein (BASECRP), calprotectin (CALPRO), concomitant immunomodulator use (RDCI). The “proc logistic” routine in SAS was implemented with an automated forward selection and backward elimination (alpha = 0.05, entry criteria = 0.1 and elimination criteria = 0.05).

Table 18 through Table 21 shows that no significant exposure-response relationships were identified for either clinical remission or enhanced clinical response in either study c13007 or study c13011 and across weeks 6, 10, 14, and 52. It is possible that the data are too limited to demonstrate significance for exposure. However, the inconsistent direction of the slopes for exposure-response in the univariate analysis and inconsistent set of predictors of response in the multivariate analysis suggest that the data are too variable to conclude a significant relationship exists.

Table 18. Multivariate Analysis of Study c13007 indicates there is no significant exposure-response relationship for clinical remission. Significant predictors of clinical remission are shown with their corresponding parameter estimates.

Analysis of Maximum Likelihood Estimates							Odds Ratio Estimates			
	Parameter	DF	Estimate	Standard	Wald	Pr > ChiS	Effect	Point Estimate	95% Wald	
				Error	Chi-Square	q			Confidence Limits	
Week 6	Intercept	1	2.9689	1.186	6.2666	0.0123				
	BASECDAI	1	-0.0156	0.00406	14.7376	0.0001	BASECDAI	0.985	0.977	0.992
Week 10	Intercept	1	0.8653	0.9858	0.7705	0.3801				
	RDCSTER (N)	1	-0.4169	0.1965	4.501	0.0339	RDCSTER N vs Y	0.434	0.201	0.938
	BASECDAI	1	-0.0076	0.00316	5.7847	0.0162	BASECDAI	0.992	0.986	0.999
Week 14	Intercept	1	3.6823	0.6147	35.8868	<.0001				
	SEX (F)	1	-0.22	0.1101	3.9928	0.0457	SEX F vs M	0.644	0.418	0.992
	RDTNF (N)	1	0.2465	0.1095	5.0728	0.0243	RDTNF N vs Y	1.637	1.066	2.515
	BASECDAI	1	-0.0131	0.00195	45.4719	<.0001	BASECDAI	0.987	0.983	0.991
Week 52	Intercept	1	1.7965	0.5764	9.7147	0.0018				
	RDTNF (N)	1	0.2763	0.1088	6.4487	0.0111	RDTNF N vs Y	1.738	1.134	2.662
	BASECDAI	1	-0.00763	0.0018	17.8746	<.0001	BASECDAI	0.992	0.989	0.996
	RDCI (N)	1	-0.2775	0.1129	6.0433	0.014	RDCI N vs Y	0.574	0.369	0.894

Table 19. Multivariate Analysis of Study c13011 indicates there is no significant exposure-response relationship for clinical remission. Significant predictors of clinical remission are shown with their corresponding parameter estimates.

Analysis of Maximum Likelihood Estimates							Odds Ratio Estimates			
	Parameter	DF	Estimate	Standard	Wald	Pr > ChiS	Effect	Point Estimate	95% Wald	
				Error	Chi-Square	q			Confidence Limits	
Week 6	Intercept	1	-1.0537	0.1935	29.6559	< 0001				
	RDTNF	1	0.5304	0.1935	7.5155	0.0061				
Week 10	Intercept	1	-0.7758	0.1587	23.9069	< 0001	RDTNF N vs Y	2.889	1.353	6.168

Table 20. Multivariate Analysis of Study c13007 indicates there was no significant exposure-response relationship for enhanced clinical response. Significant predictors of enhanced clinical response are shown with their corresponding parameter estimates.

Analysis of Maximum Likelihood Estimates						Odds Ratio Estimates			
	Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Effect	Point Estimate	95% Wald Confidence Limits
Week 6	Intercept	1	-0.686	0.1576	18.9579	<.0001			
	RDTNF (N)	1	0.496	0.1576	9.9092	0.0016	RDTNF N vs Y	2.696	1.454 5.001
Week 10	Intercept	1	-2.4627	0.8307	8.7899	0.003			
	SEX (F)	1	-0.3818	0.1624	5.5238	0.0188	SEX F vs M	0.466	0.247 0.881
	INADTNF (N)	1	0.6412	0.2049	9.7956	0.0017	INADTNF N vs Y	3.605	1.615 8.048
	BASECDAI	1	0.00594	0.00246	5.8316	0.0157	BASECDAI	1.006	1.001 1.011
Week 14	BASECRP	1	-0.0176	0.00775	5.1687	0.023	BASECRP	0.983	0.968 0.998
	Intercept	1	0.6254	0.1396	20.0703	<.0001			
	BASEEIS	1	-0.0126	0.00581	4.7385	0.0295	BASEEIS	0.987	0.976 0.999
Week 52	Intercept	1	0.7967	0.5258	2.2961	0.1297			
	RDTNF (N)	1	0.3321	0.1029	10.4232	0.0012	RDTNF N vs Y	1.943	1.298 2.907
	BASECDAI	1	-0.00327	0.0016	4.1523	0.0416	BASECDAI	0.997	0.994 1
	RDCI (N)	1	-0.32	0.108	8.7739	0.0031	RDCI N vs Y	0.527	0.345 0.805

Table 21. Multivariate Analysis of Study c13011 indicates there was no significant exposure-response relationship for enhanced clinical response. Significant predictors of clinical remission are shown with their corresponding parameter estimates.

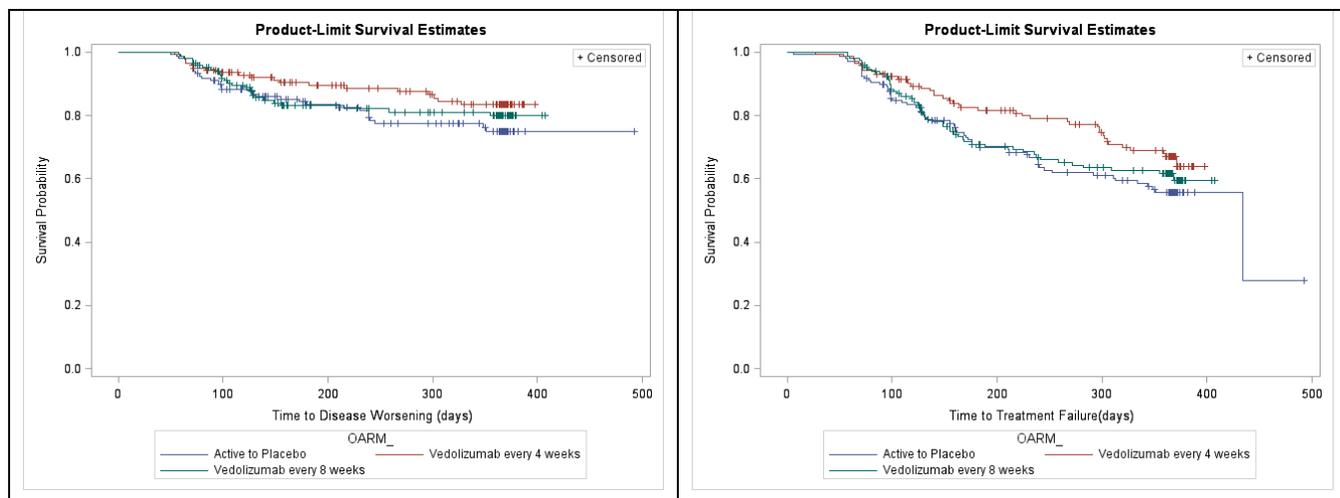
Analysis of Maximum Likelihood Estimates						Odds Ratio Estimates			
	Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Effect	Point Estimate	95% Wald Confidence Limits
Week 6	Intercept	1	-3.0278	1.0278	8.6778	0.0032			
	SEX (F)	1	-0.3344	0.1557	4.614	0.0317	SEX F vs M	0.512	0.278 0.943
	BASECDAI	1	0.00865	0.00325	7.0713	0.0078	BASECDAI	1.009	1.002 1.015
Week 10	Intercept	1	0.087	0.1476	0.3476	0.5555			

Time to disease worsening or treatment failure:

Time to disease worsening or treatment failure was evaluated previously for other products for the treatment of UC and/or CD and was included as an exploratory efficacy endpoint in the vedolizumab development program. Further, the results for study c13007 (Figure 25) suggest an increased duration of treatment benefit with the more frequent dosing regimen, Q4W, compared to the Q8W regimen. This begs the question of whether a higher dose is appropriate to achieve a longer treatment benefit. Univariate and multi-variate time-to-event analysis were conducted to ascertain if an exposure-response relationship existed for time to disease worsening or time to treatment failure.

Figure 25. Duration of response (Time to disease worsening or Time to treatment failure) is greater for the Q4W dosing group compared to the Q8W and placebo dose groups in Trial c13007.

Time to Disease Worsening:	Time to Treatment Failure:
----------------------------	----------------------------



In order to account for potential confounding factors, a multivariate Cox-proportional hazards model was evaluated for potential effects of mean trough concentration, sex, age, race, prior disease duration (CDDUR), region of GI tract where disease is located (LOCALIZE), concomitant corticosteroid use (RDCSTER), prior failure/naive to TNF (RDTNF), inadequate response to prior TNF treatment (INADTNF), baseline CDAI score (BASECDAI), baseline EI manifestations score (BASEEIS), baseline HBI (BASEHBI), baseline C-reactive protein (BASECRP), calprotectin (CALPRO), concomitant immunomodulator use (RDCI). Results of this analysis are shown in Table 22.

Table 22. Final model estimates for multivariate Cox-proportional hazards model for time to disease worsening suggest a significant exposure response relationship.

Analysis of Maximum Likelihood Estimates									
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		
mnctrough	1	0.02137	0.0069	9.5958	0.002	1.022	1.008	1.036	
RDTNF	1	-1.19036	0.35837	11.033	0.0009	0.304	0.151	0.614	

Similar analyses were performed for time to treatment failure. No tested covariates were significant in the analysis of time to treatment failure.

Despite the positive correlation between exposure and time to disease worsening, discussions with the medical review division indicated that this exploratory endpoint was not a sufficiently robust assessment of disease status to warrant dosage adjustment.

Are week 14 efficacy results predictive of week 52 efficacy results for clinical remission and enhanced clinical response:

The following analysis is in support of Section 1.1.8.

For clinical remission: see Section 1.1.8.

For enhanced clinical response: Of the patients that did not obtain enhanced clinical response at week 14 (n = 65 for Q8W and n=59 for Q4W), 17% (n=11) remitted by week 52 for the Q8W dose group and 31% (n=18) remitted by week 52 for the Q4W dose group (Shown in Figure 12).

Multivariate logistic regression analyses were done to evaluate the predictive capability of remission or enhanced clinical response at week 14 for the probability of remission or enhanced clinical response at week 52. Multivariate logistic models were constructed in the same manner as outlined above with the addition of one more potential predictor of remission or enhanced clinical response: clinical remission or enhanced clinical response at week 14.

The Receiver Operating Characteristic (ROC) curves for these analyses are shown in (Figure 13 and Figure 27). In the case of the multivariate analysis for both clinical remission and enhanced clinical response, the occurrence of remission or enhanced clinical response at week 14 had the highest significance of any of the model covariates with a p-value < 0.0001.

Figure 26. If enhanced clinical response is not achieved by week 14, there is an 17 – 31% chance that subject will remit by week 52.

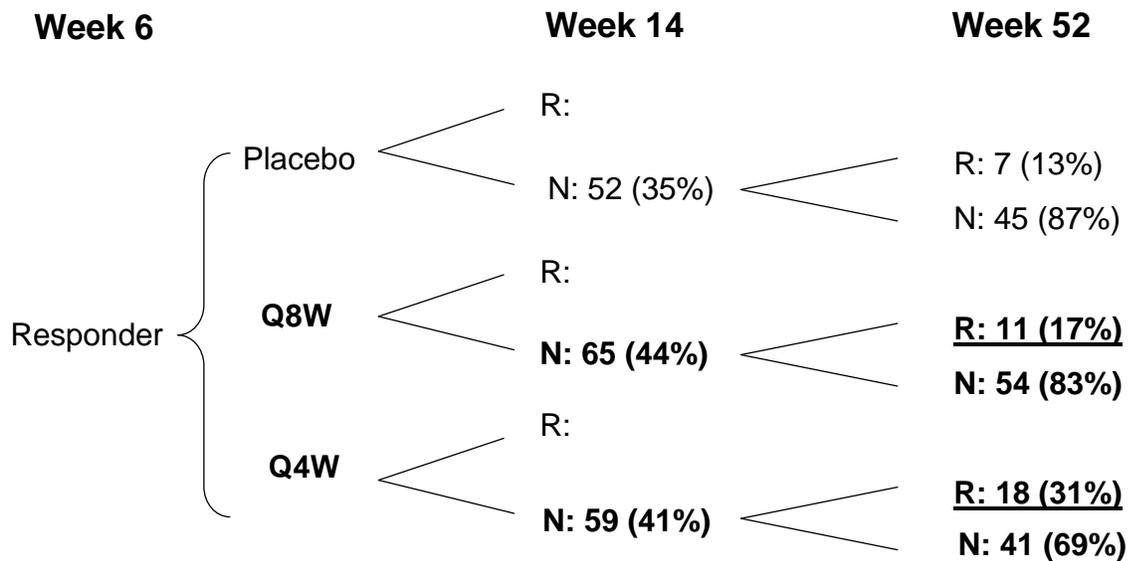
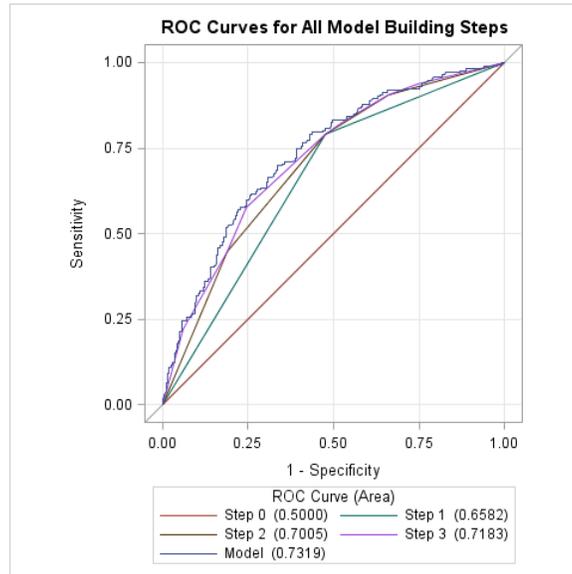


Figure 27. ROC curves for the predictive capability of enhanced clinical response at week 14 for the probability of enhanced clinical response at week 52. The graph depicts results for the multivariate analysis. Steps 1-3 and 'model' are the ROC curves for each step of the model building procedure which consisted of forward selection of 4 covariates (ECR_wk14, RDTNF, and RDCI, BASECDAI), the first being enhanced clinical response at week 14. The final model ROC curve is indicated by the dark blue line.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER_UC_c13006.sas	Ulcerative Colitis Analysis Code	..\Reviews\PM Review Archive\2013\Vedolizumab_BLA125476_JCE\ER Analyses\Ulcerative Colitis\SAS code
ER_CD_c13007_ITT.sas	Crohn's Disease Analysis Code	..\Reviews\PM Review Archive\2013\Vedolizumab_BLA125476_JCE\ER Analyses\Crohn's Disease\SAS code

**OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW**

NDA/BLA Number	BLA 125476, 125507
Submission Date	6/20/2013
Applicant Name	Millennium Pharmaceuticals
Generic Name	Vedolizumab
Proposed Indication	Ulcerative Colitis and Crohn's Disease
Primary Reviewer	Sarah Dorff, Ph.D.
Secondary Reviewer	Mike Pacanowski, Pharm.D., M.P.H.

1 Background

Vedolizumab is a humanized monoclonal antibody directed against $\alpha 4\beta 7$ integrin developed for the treatment of patients with ulcerative colitis (UC) and Crohn's disease (CD). Inhibition of the $\alpha 4\beta 7$ integrin, which is found on a discrete subset of lymphocytes, prevents lymphocyte adhesion to mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and lymphocyte invasion of endothelial cells. Disruption of the $\alpha 4\beta 7$ /MAdCAM-1 binding in the gut leads to a decrease in the aberrant inflammatory response characteristic of patients with UC and CD.

Numerous genetic factors underlie susceptibility to inflammatory bowel disease (IBD). To date, 163 loci have been associated with IBD (UC or CD), and a majority of these loci are shared by UC and CD (110/163, 30 CD-specific and 23 UC-specific; PMID: 21677747, 23128233). The applicant evaluated genetic variations in 8 gene regions in a Phase 2 trial. The purpose of this review is to determine whether those genetic variations affect clinical response to treatment with vedolizumab.

2 Submission Contents Related to Genomics

The vedolizumab development program consisted of 19 studies including 7 Phase 1 trials, 8 phase 1b/2 trials, and 4 phase 3 trials. DNA was collected in one phase 2 trial in UC (C13002) and three phase 3 trials in UC and CD (C13006, C13007, and C13011). The applicant sequenced the 46 subjects enrolled in the phase 2 multiple ascending dose (2.0-10.0 mg/kg) trial (C13002) for 14 genetic variants in the following gene regions: *NOD1*, *NOD2*, *MADCAM1*, *ITGB7*, *SLC22A4*, *CARD8*, *IL23R*, and IBD5. The applicant chose SNPs based on previously observed associations with IBD or potential relevance to the mechanism of vedolizumab. Of the 44 subjects for whom subject-level data were submitted, 35 received treatment with vedolizumab (N = 12, 11, and 12 for vedolizumab doses of 2.0, 6.0, and 10.0 mg/kg, respectively, with 9 subjects receiving placebo). Analysis of the effects of variants in the selected genes on clinical response to vedolizumab was a specified exploratory objective for this study. The results are included in the clinical study report for C13002.

The sponsor has not proposed any labeling based on the pharmacogenetic aspect of this study.

Reviewer comment: The applicant did not specify the details of the genotyping method used (primers, conditions, etc.) or accuracy. A clear rationale for selecting the various markers

(given the myriad other variants that are associated with IBD) was not provided, but these appear to be reasonably complete given the pharmacology of vedolizumab. Routine clinical practice does not include genetic testing for any of these markers.

3 Key Questions and Summary of Findings

3.1 Does genetic variation impact clinical response to vedolizumab?

Clinically relevant effects of SNPs within the genes NOD1, NOD2, MADCAM1, ITGB7, SLC22A4, CARD8, IL23R and the IBD5 locus on vedolizumab response were not observed in subjects with UC.

3.1.1 Applicant's analysis

The frequencies of the 14 SNPs in the 8 genes are summarized in table 1. The applicant concluded that the frequencies of each SNP were similar to those observed in other studies that have included both UC and healthy subjects.

Table 1. Applicant Provided Genotyping Results in Study 13002 Full Analysis Set (N = 46)

SNP Segment	n (%)	AA	AC	AG	AT	CC	CG	CT	GG	TT
IL23R_a rs11209026 (a)				3 (7)					41 (93)	
IL23R_b rs1004819 (b)						21 (48)		19 (43)		4 (9)
IL23R_c rs10889677 (c)	6 (14)		19 (43)			19 (43)				
NOD1 rs2907748 (b)						29 (66)		13 (30)		2 (5)
NOD2_Arg rs2066844 (b)						42 (95)		2 (5)		
NOD2_Gly rs2066845 (d)							1 (2)		43 (98)	
SLC22A4 rs1050152 (b)						13 (30)		25 (57)		6 (14)
MADCAM1 rs3745925 (c)	2 (5)		20 (45)			22 (50)				
CARD8 rs2043211 (e)	18 (41)				21 (48)					5 (11)
IBD5 rs6596075 (d)						35 (80)	7 (16)		2 (5)	
ITGB7_672 rs11539433 (b)						42 (95)		2 (5)		
NOD2_1007 rs5743293 (b)								4 (9)		40 (91)
ITGB7_200 (b)						44 (100)				
ITGB7_213 rs11574537 (c)						44 (100)				

For a given SNP, there are only 3 possible genotypes.

a Possible genotypes - AA AG GG

b Possible genotypes - TT CT CC

c Possible genotypes - AA AC CC

d Possible genotypes - CC CG GG

e Possible genotypes - AA AT TT

Percents are based on the number of patients who had genotyping performed. Results reflect samples taken at screening.

Reference: Study 13002, Appendix 14.1.5.1.

Reviewer comment: The applicant did not perform any analyses of genotype effects on clinical endpoints because of the small sample size; genotype distributions were calculated for descriptive purposes.

3.1.2 Reviewer's analysis

Allele frequencies were calculated for all available study subjects (N = 44) and vedolizumab treated study subjects (N = 35) for comparison to minor allele frequencies (MAFs) reported in dbSNP (Table 2). Two SNPs in the *ITGB7* gene were not informative in the study population. MAFs in the remaining 12 SNPs were consistent with those publically reported. Exploratory analysis of genotype associations with clinical response at day 113, defined as a decrease from baseline in the partial Mayo score ≥ 2 points and $\geq 25\%$, as well as a decrease in rectal bleeding

subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1, was performed using logistic regression. Day 113 was chosen as the first study visit following final vedolizumab dose on day 85 and clinical response data were reasonably complete (1 subject missing). Study arm (i.e. vedolizumab dose) was not associated with clinical response. Treatment with vedolizumab resulted in an overall clinical response rate of 73.5% (25/34) on day 113. No large effect of any genetic variant on clinical response to vedolizumab was observed (Table 2).

Table 2. Reviewer Calculated Allele Frequencies and Clinical Response by Genotype for Study 13002

Gene	Identifier	Minor Allele	MAF (N=44)	MAF (N=35)	MAF dbSNP (CEU)	Clinical Response on Day 113, Pooled Vedolizumab Arms n/N (%)		
						AA ^a	Aa ^a	aa ^a
<i>IL23R</i>	rs11209026	A	0.03	0.01	0.04	24/33 (72.7%)	1/1 (100.0%)	0/0 (0.0%)
<i>IL23R</i>	rs1004819	T	0.31	0.27	0.29	11/15 (73.3%)	12/16 (75.0%)	2/3 (66.7%)
<i>IL23R</i>	rs10889677	A	0.35	0.32	0.29	11/13 (84.6%)	10/16 (62.5%)	4/5 (80.0%)
<i>NOD1</i>	rs2907748	T	0.19	0.15	0.29	17/23 (73.9%)	7/9 (77.8%)	1/2 (50.0%)
<i>NOD2</i>	rs2066845	C	0.01	0.01	-	25/33 (75.8%)	0/1 (0.0%)	0/0 (0.0%)
<i>SLC22A4</i>	rs1050152	T	0.28	0.34	0.40	7/11 (63.6%)	12/17 (70.6%)	6/6 (100.0%)
<i>MADCAM1</i>	rs3745925	A	0.27	0.22	0.17	13/18 (72.2%)	11/14 (78.6%)	1/2 (50.0%)
<i>CARD8</i>	rs2043211	T	0.35	0.28	0.27	9/14 (64.3%)	12/16 (75.0%)	4/4 (100.0%)
<i>IBD5</i>	rs6596075	G	0.13	0.06	0.18	21/29 (72.4%)	4/5 (80.0%)	0/0 (0.0%)
<i>ITGB7</i>	rs11539433	T	0.02	0.02	0.02	23/32 (71.9%)	2/2 (100.0%)	0/0 (0.0%)
<i>NOD2</i>	rs5743293	C	0.05	0.03	-	23/31 (74.2%)	2/3 (66.7%)	0/0 (0.0%)

^a AA, Aa, and aa refer to homozygous for the major allele, heterozygous, and homozygous for the minor allele, respectively; uninformative SNPS (NOD2 rs2066844, ITGB7_200, and ITGB7 rs11574537) are not included
Data Source: Study C13002, Listing 16.2.4.9B.

Reviewer comment: Few of the genetic markers tested had sufficient numbers of subjects to evaluate differences in clinical response rates. SLC22A6 and CARD8 tended to show higher response rates in subjects carrying one or two minor alleles. Neither of these have a clear biological basis for the observed difference.

4 Summary and Conclusions

Several genetic variations have been strongly associated with susceptibility to CD and UC. The applicant evaluated variation within 8 gene regions (*NOD1*, *NOD2*, *MADCAM1*, *ITGB7*, *SLC22A4*, *CARD8*, *IL23R* and the *IBD5* loci) that were purported to have potential relevance to IBD or the mechanism of vedolizumab in subjects with UC. The observed allele frequencies in

this study were similar to those previously reported. No associations between any SNP and clinical response were observed. The sample size was too small to draw meaningful conclusions.

5 Recommendations

The analyses submitted by the sponsor are exploratory in nature. No additional action is required at this time.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

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/s/

LANYAN FANG
11/08/2013

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11/08/2013

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HAE YOUNG AHN
11/08/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125476

Applicant: Millennium

Stamp Date: 6/20/2013

Drug Name: Vedolizumab

Submission Type: NME

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		The drug product used in the pivotal trials is the same as the to-be-marketed drug product. The comparability data were submitted comparing the drug product used in the pivotal clinical trials and those used in the Phase I/II clinical trials
2	Has the applicant provided metabolism and drug-drug interaction information?		X		Vedolizumab is mAb and not metabolized by CYP enzymes in the liver. DDI potential is a review issue.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the BLA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the BLA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Weight-based dosing was explored by the sponsor and concluded it is not necessary
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Not indicated for pediatric patients
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Request pediatric waiver (b) (4) years) and deferral (b) (4)
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

Please convey the below IR to the sponsor:

- 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.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u><i>General Information About the Submission</i></u>				
	Information			Information
NDA/BLA Number	125-476	Brand Name		
OCP Division (I, II, III, IV, V)	DCP III	Generic Name		Vedolizumab
Medical Division	DGIEP	Drug Class		Recombinant human IgG1
OCP Reviewer	Lanyan Fang, Ph.D.	Indication(s)		UC and CD
OCP Team Leader	Yow-Ming Wang, Ph.D.	Dosage Form		Lyophilized powder
Pharmacometrics Reviewer	Justin Earp, Ph.D.	Dosing Regimen		300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter. 300 mg Q4W for decreased or loss of response.
Date of Submission	6/20/2013	Route of Administration		I.V.
Estimated Due Date of OCP Review		Sponsor		Millennium
Medical Division Due Date		Priority Classification		Priority
PDUFA	2/18/2014	Dosing Strength		300 mg/vial
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Reference Bioanalytical and Analytical Methods	X	10		3 for vedolizumab PK; 3 for PD markers; 4 for ADA assays
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	7		BW based dosing & fixed dose
multiple dose:				
Patients-				
single dose:	X	1		
multiple dose:	X	11		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			popPK assessment
Age:	X			popPK assessment
pediatrics:				Request deferral and waiver
geriatrics:				
renal impairment:				
hepatic impairment:				
Immunogenicity:	X			
PD -				
Phase 2:	X			
Phase 3:	X			
PK/PD -				

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:	X			Meta analysis
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability	X			Study C13010 Not relevant as intended IV use only
Relative bioavailability -				
solution as reference:				IV use only
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
PK and PD comparability:	X			Study C13009
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X			
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies		29		19 clinical pharm/clinical studies and 10 bioanalytical reports

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing memo

MOA and Indication:

This is an original BLA for vedolizumab, a new molecular entity, which is a humanized monoclonal antibody that binds exclusively to the $\alpha 4\beta 7$ integrin on pathogenic gut-homing lymphocytes and selectively inhibits adhesion of these cells to mucosal addressin cell adhesion molecule 1 (MAdCAM 1) but not vascular cell adhesion molecule 1 (VCAM 1). The $\alpha 4\beta 7$ integrin is expressed on the surface of a discrete subset of memory T-lymphocytes that preferentially migrate into the gastrointestinal tract and can cause inflammation that is characteristic of ulcerative colitis and Crohn's disease.

The proposed indication is for the treatment of moderately to severely active Crohn's disease and ulcerative colitis (UC) in adult patients who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF α) antagonist.

Product and Proposed Dose:

Three processes of MLN0002, representing differences in the manufacturing process and/or formulation of the drug substance (DS) and drug product (DP), have been used in nonclinical evaluations and in the clinical development program and are identified as MLN0002 (Process A), MLN0002 (Process B), and MLN0002 (Process C). MLN0002 (Process C) was the formulation used throughout phase 3 clinical trials and is the intended commercial material. PK comparability between Process B and C was assessed in Study C13009 and the PK appeared comparable.

The proposed dosage form is a lyophilized cake available in sterile single-use vials containing 300 mg of vedolizumab for intravenous use. The proposed dosing regimen is: initial dose of 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Some patients who have experienced a lack of response or decrease in their response may benefit from an increase in dosing frequency to 300 mg every four weeks. The proposed dose regimen was examined in the Phase 3 trials, basing on the results from Phase 2 dose ranging trials (C13002 for UC and L299-016 for CD). Shallow exposure-response relationship was observed in the Phase 3 data (both UC and CD indications) and the appropriateness of proposed dose will be a review issue.

PK/PD:

The PK of vedolizumab was characterized in both healthy and subjects with UC or CD receiving Process B or C drug products. The impact of intrinsic factors such as gender and age on the PK of vedolizumab was assessed by population PK approach. During the clinical development program, vedolizumab was dosed initially on a body weight-adjusted (mg/kg) basis, and subsequently on a fixed-dose basis (mg) based on the results of Study C13005 showing only a slight trend of decreasing Vedolizumab exposure with increasing body weight. The appropriateness of fixed dose will be a review issue. No dose adjustment was recommended based on the population PK approach.

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PD markers including fecal calprotectin, C-reaction protein, receptor occupancy, and CD4+ and CD8+ trafficking were explored in the clinical studies. (b) (4)

Genetic Variation Impact

The sponsor collected DNA samples in Studies C13002, C13006, C13007, and C13011. Only samples from Study C13002 have been analyzed for single nucleotide polymorphisms (SNPs). Due to limited sample size, the relationship between the selected SNPs and outcome were not determined. The validity of the pharmacogenomics data will be a review issue.

DDI assessment

No dedicated clinical studies were conducted to evaluate the effect of co-administered drugs on the pharmacokinetics of vedolizumab. The potential for concomitant immunomodulators therapies to cause drug-drug interactions were evaluated using population pharmacokinetics approach using data from phase 3 studies. The sponsor didn't conduct any studies or assessment to evaluate the potential of vedolizumab as a perpetrator on drugs metabolized by CYP enzymes even though we conveyed the below comment during the pre-BLA meeting to the sponsor:

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.

Therefore, the DDI potential of vedolizumab will be a review issue.

Immunogenicity

The immunogenicity incidence and the impact of immunogenicity on PK, efficacy and safety were assessed in the Phase 3 studies. The assessment of immunogenicity incidence and its impact on PK/efficacy/safety will be a review issue.

Overall Clinical Program

A total of 19 clinical studies have been conducted, of which 7 were phase 1 studies conducted in healthy subjects, 8 were phase 1b/2 studies conducted in patients with UC or CD, and 4 were phase 3 studies (C13006, C13007, C13011 and C13008) conducted in patients with UC or CD. An overview of the clinical studies conducted during development program of vedolizumab is attached in the Appendix.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III does not find any issues related to its fileability.

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Appendix: List of studies (sponsor's Table 2-2 from the summary of clin pharm findings)
Table 2-2 Clinical Pharmacology and Biopharmaceutic Studies in Patients and Healthy Subjects

Study Number	Study Title	Objectives	Demographics	Number of Subjects (ITT) Number of Subject with PK	Duration, Dosing Regimens, Process
Biopharmaceutic Studies – Comparative Bioavailability (BA) and Bioequivalence (BE)					
C13009	A Phase 1 Single Dose Study to Determine the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of a Lyophilized Formulation (Process C Drug Product) of MLN0002 in Healthy Subjects	<ul style="list-style-type: none"> PK α, β saturation PK and PD Comparability of Process B and Process C Safety and tolerability QT/QTc evaluation 	M/F: 47 (54%)/40 (46%) Mean age: 29.6 yrs (range 19-45) Race: <ul style="list-style-type: none"> 64 (74%) White 14 (16%) Black 2 (2%) Hawaii 1 (1%) Other Ethnicity: <ul style="list-style-type: none"> 3(3%) Hispanic 84 (97%) Not Hispanic Mean weight: 74.97 kg (range 49.7-113.2)	Total = 87 VDZ = 62 Placebo = 25 PK = 55 Intensive	Single dose, Process B & C 300 mg IV, Process C 600 mg IV, Process C 600 mg IV, Process B Placebo
Human Pharmacokinetics (PK) Studies					
Healthy Subjects PK and Initial Tolerability					
C13001	A Phase 1, Single Ascending Dose, Randomized, Placebo-Controlled, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MLN0002 in Healthy Subjects	<ul style="list-style-type: none"> Safety and tolerability PK PK/PD relationship α, β saturation 	M/F: 27 (55%)/ 22 (45%) Mean age: 44.7 yrs (range 21-63) Race: <ul style="list-style-type: none"> 49 (100%) White Ethnicity: <ul style="list-style-type: none"> 3(6%) Hispanic 46 (94%) Non Hispanic Mean weight: 73.09 (50.2, 92.8)	Total = 49 VDZ = 39 Placebo = 10 PK=32	Single dose, Process B 0.2 mg/kg IV (n = 8) 0.5 mg/kg IV (n = 7) 2.0 mg/kg IV (n = 8) 6.0 mg/kg IV (n = 8) 10.0 mg/kg IV (n = 8) Placebo IV (n = 10)
Healthy Subjects PK and Initial Tolerability Studies (UC or CD)					
Study Number	Study Title	Objectives	Demographics	Number of Subjects (ITT) Number of Subject with PK	Duration, Dosing Regimens, Process
C13010	A Phase 1 Study of the Bioavailability of MLN0002 Administered by Subcutaneous and Intramuscular Injection to Healthy Male Subjects	<ul style="list-style-type: none"> SC bioavailability of 180 mg VDZ IM bioavailability of 180 mg VDZ Safety of SC and IM administered VDZ PK Immunogenicity 	M/F: 42 (100%)/0 Mean age: 33 yrs (range 18-57) Race: <ul style="list-style-type: none"> 31 (74%) White 8 (19%) Black 1 (2%) Native Hawaiian or Other Pacific Islander 1 (2%) Asian 1 (2%) Other Ethnicity: <ul style="list-style-type: none"> 1 (2%) Hispanic or Latino 41 (98%) Not Hispanic or Latino Mean BMI: 26.20 (range 21.2-30.8)	Total = 42 VDZ = 42 PK=42	Single dose, Process C 180 mg SC (n = 14) 180 mg IM (n = 14) 180 mg IV (n = 14)
Patient PK and Initial Tolerability Studies (UC or CD)					
L297-005	A Phase 1b/2a Randomized, Placebo-Controlled, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Effectiveness of LDP-02 in Subjects with Severe Ulcerative Colitis	<ul style="list-style-type: none"> Safety and tolerability PK α, β saturation Efficacy 	M/F: 6 (67%)/3 (33%) Median age: 42.1 (range 25.2, 77.4) Race: <ul style="list-style-type: none"> 8 (89%) Caucasian 1 (11%) Black Median weight: 65.6 kg (range 52.0-77.9)	Total = 14 VDZ = 9 Placebo = 5 PK=9	2 doses (Days 1 and 15), Process A 0.15 mg/kg IV (n = 5) 0.5 mg/kg IV (n = 4) 2.0 mg/kg IV (n = 0) Placebo IV (n = 5)
L297-006	A Single Dose Phase 1b/2a Placebo-Controlled, Randomized, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics,	<ul style="list-style-type: none"> Safety and tolerability PK α, β saturation Efficacy 	M/F: 12 (57%)/9 (47%) Median age: 41.0 yrs (range 22-77) Race:	Total = 29 VDZ = 21 Placebo = 8	Single dose, Process A 0.15 mg/kg SC (n = 5) 0.15 mg/kg IV (n = 5) 0.5 mg/kg IV (n = 5) 2.0 mg/kg IV (n = 6)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study Number	Study Title	Objectives	Demographics	Number of Subjects (ITT) Number of Subject with PK	Duration, Dosing Regimens, Process
	Pharmacodynamics and Effectiveness of LDP-02 in Patients with Moderately Severe Ulcerative Colitis		<ul style="list-style-type: none"> • 21 (100%) Caucasian Ethnicity: not available Median weight: 78.1 kg (range 48.8-94.0)	PK=21	Placebo SC or IV (n = 8)
C13004	A Phase 2, Multiple Dose, Open-Label Study to Determine the Long-Term Safety of MLN0002 in Patients with Ulcerative Colitis and Crohn's Disease	<ul style="list-style-type: none"> • Long-term safety 	M/F: 29 (40%)/43 (60%) Median age: 41.0 yrs (range 19-74) Race: <ul style="list-style-type: none"> • 71 (99%) White • 1 (1%) American Indian Ethnicity: <ul style="list-style-type: none"> • 71 (99%) Not Hispanic or Latino • 1 (1%) Not Reported Median weight: 74.65 kg (range 41.8-130.4)	Total = 72* VDZ = 72* (No placebo) PK= 46	12 doses, Process B 2 mg/kg IV Q8W 6 mg/kg IV Q8W
Intrinsic Factors PK Study – Body Weight					
C13005	A Phase 1, Single Dose, Open-Label Study to Determine the Pharmacokinetics, Safety, and Tolerability of MLN0002 in Healthy Subjects Across a Range of Low and High Body Weights	<ul style="list-style-type: none"> • PK in low and high body weight • Safety and tolerability 	M/F: 11 (42%)/15 (58%) Mean age: 32.0 yrs (range 19-57) Race: <ul style="list-style-type: none"> • 17 (65%) White • 7 (27%) Black • 2 (8%) Native Hawaiian Ethnicity: <ul style="list-style-type: none"> • 3 (12%) Hispanic • 23 (88%) Non Hispanic Mean weight: 90.15 (46.0, 129.7)	Total = 26 VDZ = 26 PK=23	Single dose, Process B 6 mg/kg IV
Human Pharmacodynamic Studies					
Healthy Subject PD and PK/PD Studies					
L297-007	A Placebo Controlled, Double-Blind, Rising Dose Study Investigating the Tolerability, Pharmacodynamics and Pharmacokinetics Of LDP-02 Given by the Subcutaneous and Intravenous Routes in Healthy Male Volunteers	<ul style="list-style-type: none"> • Safety and tolerability • PK • Immunogenicity • $\alpha_4\beta_7$ saturation • effect on cytokine levels 	M/F: 19 (100%)/0 Mean age: 29 yrs (range 19-46) Race: <ul style="list-style-type: none"> • 15 (79%) Caucasian • 3 (16%) Negroid • 1 (5%) Asian Mean weight: 76.8 kg (range 62.6- 104.5)	Total = 19 VDZ = 14 Placebo = 5 PK=14	Single dose, Process A 0.15 mg/kg IV (n = 3) 0.15 mg/kg SC (n = 3) 0.5 mg/kg IV (n = 3) 1.5 mg/kg IV (n = 3) 2.5 mg/kg IV (n = 2) Placebo SC or IV (n = 5)
C13012	A Phase 1 Single-Arm Study to Evaluate the Effects of a Single Intravenous Dose of Vedolizumab (MLN0002) on the CD4 ⁺ :CD8 ⁺ Lymphocyte Ratio in the Cerebrospinal Fluid of Healthy Subjects	<ul style="list-style-type: none"> • Evaluate effect of VDZ on: <ul style="list-style-type: none"> o CSF CD4⁺:CD8⁺ lymphocyte ratio o CSF CD4⁺ and CD8⁺ lymphocyte counts o Peripheral blood 	M/F: 10 (71%)/4 (29%) Mean age: 26.9 yrs (range 19-41) Race: <ul style="list-style-type: none"> • 10 (71%) White • 3 (21%) Black • 1 (71%) Other Ethnicity	Total = 14 VDZ = 14 PK=14 Intensive	Single dose, Process C 450 mg IV

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Study Number	Study Title	Objectives	Demographics	Number of Subjects (ITT) Number of Subject with PK	Duration, Dosing Regimens, Process
		<ul style="list-style-type: none"> CD4+ and CD8+ lymphocytes counts Safety and tolerability Distribution of VDZ into CSF 	<ul style="list-style-type: none"> 2 (14%) Hispanic 12 (86%) Not Hispanic Mean weight: 74.3 kg (range 58.6-90.2)		
C13013	A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, Single Dose Study in Healthy Subjects to Determine the Immune response to Systemic and Mucosal Antigenic Challenge in the Presence of vedolizumab	<ul style="list-style-type: none"> Determine rates of seroconversion to a hepatitis B vaccine series Determine the rates of seroconversion to an oral cholera vaccine series Assess change in hepatitis B surface antibody Safety and tolerability 	M/F: 87(69%)/40 (31%) Mean age: 27.5 yrs (range 19-39) Race: <ul style="list-style-type: none"> 118 (93%) White 2 (2%) Black 3 (2%) Asian 4 (3%) Other Ethnicity: <ul style="list-style-type: none"> 1 (<1%) Hispanic 126 (99%) Not Hispanic Mean weight: 75.6 kg (range 47.9-112.5)	Total = 127 VDZ = 64 Placebo = 63 PK=63 <div style="border: 1px solid black; background-color: #f4a460; padding: 2px; display: inline-block;">Intensive</div>	Single dose, Process C 750 mg IV
Patient PD and PK/PD Studies					
		<ul style="list-style-type: none"> Safety and tolerability Efficacy PK and PD 	M/F: 56 (44.1%)/71 (55.9%) Median age: 36.0 yrs (range 18-71) Race: <ul style="list-style-type: none"> 120 (94.5%) Caucasian 2 (1.6%) Black 4 (3.1%) Other Ethnicity: 0% Median weight: 70.5 kg (range 36.4-119.5)	Total = 185 VDZ= 127 Placebo = 58 PK=21	2 doses (Days 1 and 29), Process A 0.5 mg/kg IV (n = 62) 2.0 mg/kg IV (n = 65) Placebo IV (n = 58)
M200-021	A Phase 1/2, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Multicenter Study to Determine the Safety, Pharmacokinetics, and Effectiveness of Multiple Doses of LDP-02 in Patients with Mildly to Moderately Active Ulcerative Colitis	<ul style="list-style-type: none"> Safety and tolerability PK and PD Efficacy 	M/F: 13 (54%)/11 (46%) Median age: 41.0 yrs (range 26-67) Race: <ul style="list-style-type: none"> 20 (83%) White 4 (17%) Black Ethnicity: not available Median weight: 79.6 kg (range 52.1-102.7)	Total = 30 VDZ = 24 Placebo = 6 PK=24	2 doses (Days 1 and 29), Process A 0.5 mg/kg IV (n = 12) 2.0 mg/kg IV (n = 12) Placebo IV (n = 6)
M200-022	A Phase 2, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Multicenter Study to Determine the Safety, Pharmacokinetics, and Effectiveness of LDP-02 in Patients with Mildly to Moderately Active Ulcerative Colitis	<ul style="list-style-type: none"> Efficacy Safety and tolerability PK and PD 	M/F: 63 (53%)/55 (47%) Median age: 41.0 yrs (range 19-79) Race: <ul style="list-style-type: none"> 109 (92%) White 1 (1%) Hispanic 3 (3%) Black 5 (4%) Other 	Total = 181 VDZ = 118 Placebo = 63 PK=22	2 doses (Days 1 and 29), Process A 0.5 mg/kg IV (n = 58) 2.0 mg/kg IV (n = 60) Placebo IV (n = 63)

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Study Number	Study Title	Objectives	Demographics	Number of Subjects (ITT) Number of Subject with PK	Duration, Dosing Regimens, Process
			Median weight: 71.4 (range 44.7, 135.9)		
C13002	A Phase 2, Randomized, Placebo-Controlled, Double-Blind Study to Determine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MLN0002 Following Multiple Intravenous Doses in Patients with Ulcerative Colitis	<ul style="list-style-type: none"> Safety and tolerability PK PK/PD relationship $\alpha_4\beta_7$ saturation 	M/F: 19 (41%)/ 27 (59%) Mean age: 41.0 yrs (range 19-69) Race: <ul style="list-style-type: none"> 46 (100%) White Ethnicity: <ul style="list-style-type: none"> 46 (100%) Not Hispanic or Latino Mean weight: 76.04 kg (range 42.0-123.0)	Total = 47 VDZ = 38 ^b Placebo = 9 PK=35 <div style="background-color: orange; color: white; padding: 2px; text-align: center;">Intensive</div>	4 doses, Process B 2.0 mg/kg IV (n = 13) 6.0 mg/kg IV (n = 14) 10.0 mg/kg IV (n = 11) Placebo IV (n = 9)
CPH-001	Phase 1, Multiple-dose Study of MLN0002 in Patients with Ulcerative Colitis	<ul style="list-style-type: none"> PK Safety and tolerability PD Efficacy 	M/F: 7 (77.8%)/2 (22.2%) Mean age: 44.7 yrs (range 21-70) Race: <ul style="list-style-type: none"> 9 (100%) Japanese Ethnicity: Not applicable Mean weight: 69.02 kg (range 43.7-93.1)	Total = 9 Vedolizumab = 9 PK=9	3 doses (Days 1, 15 and 43) Process C 150 mg IV (n=3) 300 mg IV (n=6)
Phase 3 Efficacy and Safety Studies in Patients with UC or CD					
C13006	A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis	Induction Phase: <ul style="list-style-type: none"> Efficacy Safety PK $\alpha_4\beta_7$ saturation Immunogenicity Maintenance Phase: <ul style="list-style-type: none"> Efficacy 	M/F: 525 (59%)/370 (41%) Mean age: 40.3 yrs (range 18-78) Race: <ul style="list-style-type: none"> 73.4 (82%) White 12 (1%) Black 135 (15%) Asian 14 (2%) Other Ethnicity:	Induction Phase: <u>ITT</u> : VDZ = 225 Placebo = 149 <u>Non-ITT</u> : VDZ = 521 Maintenance Phase:	Multiple dose, Process C Induction (Weeks 0-2): <ul style="list-style-type: none"> 300 mg IV Placebo Maintenance (for 44 weeks): <ul style="list-style-type: none"> 300 mg IV Q4W 300 mg IV Q8W
		<ul style="list-style-type: none"> Safety PK $\alpha_4\beta_7$ saturation Immunogenicity Fecal calprotectin 	<ul style="list-style-type: none"> 46 (5%) Hispanic or Latino 832 (93%) Not Hispanic or Latino 17 (2%) Not reported Mean weight: 73.4 kg (range 32-174) Mean BMI: 25.1 kg/m ² (range 14-61) Mean FeC: 1868.8 μ g/g (range 23.8-20000)	<u>ITT</u> : VDZ Q4W = 125 VDZ Q8W = 122 Placebo = 126 <u>Non-ITT</u> : VDZ Q4W = 373 Placebo = 149 PK=654 <div style="background-color: orange; color: white; padding: 2px; text-align: center;">Sparse</div>	<ul style="list-style-type: none"> Placebo
C13007	A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Crohn's Disease	Induction Phase: <ul style="list-style-type: none"> Efficacy Safety PK $\alpha_4\beta_7$ saturation immunogenicity CRP Maintenance Phase: <ul style="list-style-type: none"> Efficacy Safety PK $\alpha_4\beta_7$ saturation immunogenicity 	M/F: 520 (47%)/595 (53%) Mean age: 36.1 yrs (range 18-77) Race: <ul style="list-style-type: none"> 995 (89%) White 23 (2%) Black 89 (8%) Asian 8 (<1%) Other Ethnicity: <ul style="list-style-type: none"> 26 (%) Hispanic or Latino 1065 (96%) Not Hispanic or Latino 24 (2%) Not reported Mean weight: 69.8 kg (range 30-167) Mean BMI: 23.9 kg/m ² (range 12-56) Mean CRP: 21.5 mg/L (range 0.2-295.0) Mean FeC: 1254.2 μ g/g (range	Induction Phase: <u>ITT</u> : VDZ = 220 Placebo = 148 <u>Non-ITT</u> : VDZ = 747 Maintenance Phase: <u>ITT</u> : VDZ Q4W = 154 VDZ Q8W = 154 Placebo = 153 <u>Non-ITT</u> : VDZ Q4W = 506 Placebo = 148 PK=827 <div style="background-color: orange; color: white; padding: 2px; text-align: center;">Sparse</div>	Multiple dose, Process C Induction (Weeks 0-2): <ul style="list-style-type: none"> 300 mg IV Placebo Maintenance (for 44 weeks): <ul style="list-style-type: none"> 300 mg IV Q4W 300 mg IV Q8W Placebo

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Study Number	Study Title	Objectives	Demographics	Number of Subjects (ITT) Number of Subject with PK	Duration, Dosing Regimens, Process
C13008 (ongoing)	A Phase 3, Open-label Study to Determine the Long-term Safety and Efficacy of Vedolizumab (MLN0002) in Patients with Ulcerative Colitis and Crohn's Disease	<ul style="list-style-type: none"> • Safety • Efficacy • Immunogenicity 	23.8-18607.5) M/F: 1128 (50%)/1115 (50%) Mean age: 39.1 (range 19,80) Race <ul style="list-style-type: none"> • 1981 (88%) white • 42 (2%) black • 3 (<1) Hawai or other • 185 (8%)(Asian • 3 (<1) American Indian or Alaskan • 26 (1%) other • 3 (<1) Not reported Ethnicity <ul style="list-style-type: none"> • 67 (3%) Hispanic Latino • 21.4 (95%) Not hispanic or latino • 37 (2%) not reported Mean weight: 73.2 (kg) (range 30, 173.1) Mean BMI : 24.9 (kg/m ²) (range 13.0, 59.7)	VDZ = 2443, as of 15 March 2013: <ul style="list-style-type: none"> • 1822 patients rolled over from a previous VDZ study • 421 de novo patients 	Multiple dose, Process C 300 mg Q4W open-label
C13011	A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's Disease	<ul style="list-style-type: none"> • Efficacy Safety • PK • $\alpha_4\beta_2$ saturation • Immunogenicity • CRP 	M/F: 180 (43)/236 (57) Mean age: 37.9 yrs (range 19-77) Race: <ul style="list-style-type: none"> • 374 (90%) White • 9 (2%) Black • 18 (4%) Asian • 13 (3%) Other Ethnicity: <ul style="list-style-type: none"> • 2 (1%) NR • 8 (2%) Hispanic or Latino • 403 (97%) Not Hispanic Latino • 5 (<1%) not reported Mean weight: 70.4 kg (range 40-147) Mean BMI: 24.3 kg/m ² (range 15-49) Mean CRP: 18.8 mg/L (range 0.2-168) Mean FeC: 1288.0 μ g/g (range 23.8-20000)	ITT: VDZ = 209 Placebo = 207	Multiple dose, Process C Induction (Weeks 0, 2 & 6) 300 mg IV

Abbreviations: BMI = body mass index; CD = Crohn's disease; CRP = C-reactive protein; CSF = cerebrospinal fluid; F = female; FeC = fecal calprotectin; IM = intramuscularly; ITT = intent-to-treat; IV = intravenously; M = male; PD = pharmacodynamics; PK = pharmacodynamics; Q4W = every 4 weeks; Q8W = every 8 weeks; QTc = corrected QC interval; SC = subcutaneously; UC = ulcerative colitis; VDZ = vedolizumab; yrs = years.

Gray shading denotes studies that support the label.

a 72 patients in study C13004 included 38 patients who rolled over from Study C13002; of these 38 patients, 7 had received placebo.

b One patient in the VDZ group was determined to be ineligible after randomization and was never dosed; a total 37 patients received VDZ in the study.

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/s/

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