Title: A Phase 4 Open-Label Study to Evaluate Vedolizumab IV Dose Optimization on Treatment Outcomes In Nonresponders With Moderately to Severely Active Ulcerative Colitis

NCT Number: NCT03029143

Protocol Approve Date: 19 April 2018

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
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PROTOCOL AMENDMENT

A Phase 4 Open-Label Study to Evaluate Vedolizumab IV Dose Optimization on Treatment Outcomes In Nonresponders With Moderately to Severely Active Ulcerative Colitis (ENTERPRET)

Vedolizumab IV Dose Optimization in Ulcerative Colitis

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015		
Study Number:	Vedolizumab-4014		
IND Number:	009125	**EudraCT Number:**	Not Applicable
Compound:	Vedolizumab IV		
Date:	19 April 2018	**Amendment Number:**	03

Amendment History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
02 June 2016	Initial	Not applicable	Global
19 August 2016	01	Substantial	Global
16 December 2016	02	Substantial	Global
19 April 2018	03	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center Americas Inc., sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	United States/Canada Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol and compound) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 03 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reason for this amendment is to increase the number of sites, increase the number of subjects, revise prohibited medications, clarify inclusion exclusion criteria, and document changes in study team members. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only. For specific descriptions of text changes and where the changes are located, see Appendix F.

The following is a summary of the changes made in Amendment No. 03:

1. Investigator agreement revised to remove provision of package insert.
2. Subject number to enroll was increased from 200 to 250, to randomize approximately 100 subjects.
3. Site number was increased from 70 to 80.
4. Section 5.2.2 Secondary Endpoints, Day 1 was removed from the complete Mayo score definition of Baseline.
5. Exclusion Criteria #7, clarified subjects with prior exposure to approved or investigational anti-integrin antibodies are excluded.
6. Exclusion Criteria #8, clarified subjects that previously received approved or investigational Vedolizumab (not just Vedolizumab IV) are excluded.
7. Exclusion Criteria #11, clarified timing of exclusion is during Screening.
8. Exclusion Criteria #18, clarified timing of exclusion is 2 weeks prior to Screening.
9. Exclusion Criteria #25, clarified timing of PML checklist administration.
10. Section 7.4.1 Excluded Medications was updated.
11. Section 7.4.2 Permitted Medications was updated.
12. Section 7.4.2.1 Corticosteroid Taper, co-administration maximum dose and budesonide taper were added.
13. Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject, replacement language was removed.
14. Section 8.1.2 Storage, clarified storage requirements for Vedolizumab IV.
15. Section 8.2 Investigational Drug Assignment and Dispensing Procedures, clarified lower dose will resume once serum Vedolizumab is ≤90 µg/mL.
16. Section 9.1.2 Medication History and Prior UC Disease Treatment eCRF data entry was clarified.
17. Section 9.1.3 UC Disease History, clarified eCRF data entry for UC disease as concurrent condition.

18. Section 9.1.6 Vital Sign Procedure, 5 minute period for vital sign collection and order of procedure language were removed.
19. Section 9.1.9 Documentation of Concomitant Procedures, clarified last clinic visit.
20. Section 9.1.10 Documentation of Concurrent Medical Conditions, clarified this includes lab, ECG, or physical exam abnormalities found at Screening.
21. Section 9.1.11 Procedures for Clinical Laboratory Samples, added that Screening labs may be repeated once at investigator discretion.
22. Section 9.1.19 PK Sample Collection, clarified PK samples collection timing.
23. Section 9.1.21 Tuberculosis Screening was updated to clarify Chest X-Ray should only be performed if skin or QuantiFERON tests are indeterminate.
24. Section 9.1.24 Documentation of Screen Failure, added rescreening criteria.
25. Section 9.3.1 Screening Period, period for enrollment was clarified.
26. Section 13.1.3 Efficacy Analysis, primary efficacy analysis was updated.
27. Section 13.3 Determination of Sample Size was updated to note that additional subjects may be added to account for high drop-out rates.
28. Appendix A, Prior UC disease treatment was added to the schedule of procedures.
29. Appendix A, concomitant medications was checked at Screening.
30. Appendix A, footnote (j), PK collection was clarified.
31. Appendix A, footnote (s), PML checklist administration was clarified.
32. Appendix B Responsibilities of the Investigator, added responsibility if investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** Vedolizumab IV	
Title of Protocol: A Phase 4, Open-Label Study to Evaluate Vedolizumab IV Dose Optimization on Treatment Outcomes In Nonresponders With Moderately to Severely Active Ulcerative Colitis (ENTERPRET)	**IND No.:** 009125	**EudraCT No.:** Not applicable
Study Number: Vedolizumab-4014	**Phase:** 4	
Study Design: This is a phase 4, open-label, multicenter study to investigate the efficacy and safety of dose optimization of vedolizumab IV, compared with standard dosing of vedolizumab IV, over a 30-week treatment period. This study will enroll adult subjects with moderately to severely active ulcerative colitis (UC) who are eligible for treatment with vedolizumab IV. Approximately 250 subjects will be enrolled in order to randomize approximately 100 nonresponder subjects with high vedolizumab drug clearance. All eligible subjects will receive induction therapy with vedolizumab IV 300 mg on Day 1 and Week 2 (Lead-in Period). Subjects who are assessed as having high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL) and who are nonresponders (based on partial Mayo score) at Week 6 will be randomized into the Randomized Treatment Period to receive either standard or optimized doses of vedolizumab IV. Subjects who are determined to be responders or are nonresponders at Week 6 with a Week 5 level above the predefined vedolizumab concentration threshold (≥50 µg/mL) (ie, Lead-in Failures) will not be randomized and will receive the Week 6 study drug dose and thereafter appropriate treatment per physician discretion. The study is comprised of a 28-day Screening Period, a 6-week Lead-in Period, and a 24-week Randomized Treatment Period, followed by an 18-week Follow-Up Safety Visit and a long-term follow-up (LTFU) safety survey by telephone 6 months after the last dose of study drug.		
Primary Objectives: To determine the effect of vedolizumab IV dose optimization on mucosal healing compared with the standard vedolizumab IV dosing regimen at Week 30 in subjects with UC and high vedolizumab clearance based on a predefined week 5 serum vedolizumab concentration threshold (<50 µg/mL) and who are Week 6 nonresponders.		
Secondary Objectives: To determine the effect of vedolizumab IV dose optimization on clinical response and remission compared with the standard vedolizumab IV dosing regimen at Week 30 in subjects with UC and high vedolizumab clearance based on a Week 5 predefined serum vedolizumab concentration threshold (<50 µg/mL) and who are Week 6 nonresponders.		
Subject Population: Adult subjects aged of 18 to 85 years, inclusive, with moderately to severely active UC established at least 1 month prior to Screening and who have high vedolizumab clearance based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL) and who are nonresponders at Week 6.		
Number of Subjects: Estimated total: 250 enrolled/100 randomized (50 per treatment group)	**Number of Sites:** Estimated total: Approximately 80 in the United States and Canada	
Dose Level(s): <u>Day 1 and Week 2:</u> Vedolizumab IV 300 mg (all subjects) <u>Week 6 and beyond:</u> Vedolizumab IV 300 mg every 8 weeks (Q8W), standard Vedolizumab IV 300 mg every 4 weeks (Q4W) or 600 mg Q4W (optimized)	**Route of Administration:** Intravenous	

Vedolizumab IV 300 mg Q8W (optimized arm lowest dose available following return to normalization from C_{trough} >90 µg/mL)	
Duration of Treatment: 30-week treatment period	**Period of Evaluation:** The study includes a 28-day Screening Period and a 6-week Lead-in Period. For subjects randomized to study drug, it includes a 24-week Randomized Treatment Period. All subjects are required to participate in an 18-week Follow-up Period following last dose and a LTFU safety survey by telephone, 6 months after the last dose of study drug. The duration of the study will be approximately 56 weeks.

Main Criteria for Inclusion:

- The subject has been determined to be suitable for vedolizumab IV by their physician.
- Age at Screening between 18 to 85 years of age, inclusive.
- Diagnosis of UC established at least 1 month prior to Screening.
- Active moderate to severe UC as determined by a complete Mayo score of 6 to 12 with an endoscopic subscore of ≥2 within 28 days prior to enrollment.
- Subject has had an inadequate response with, lost response to, or intolerance of at least 1 of the following agents: immunomodulator, corticosteroids, or tumor necrosis factor-alpha (TNF-α) antagonist. Subjects who are TNF-α antagonist naïve or who have failed prior TNF-α antagonist treatment (primary and secondary nonresponders or intolerant) may be included.

At Week 6, subjects must meet both of the following inclusion criteria to be eligible for randomization into the Randomized Treatment Period of the study:

- The subject is assessed as having a high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL).
- The subject is a nonresponder based on partial Mayo score at Week 6.

Main Criteria for Exclusion:

- The subject has had extensive colonic resection, subtotal or total colectomy.
- The subject has any evidence of an active infection during Screening.
- The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist during Screening or prior to the administration of the first dose of study drug on Day 1.
- The subject has received any investigational or approved biologic or biosimilar agent within 60 days or 5 half-lives prior to Screening (whichever is longer).
- The subject has had prior exposure to approved or investigational anti-integrin antibodies (eg, vedolizumab, natalizumab, efalizumab, etrolizumab, AMG-181, mucosal addressin cell adhesion molecule [anti-MAdCAM-1] antibodies, or rituximab).

Main Criteria for Evaluation and Analyses:

Primary endpoint:

- The proportion of subjects achieving mucosal healing, defined as Mayo endoscopic subscore ≤1 point, at Week 30.

Secondary endpoints:

- Proportion of subjects achieving clinical remission, where clinical remission is defined as a complete Mayo score

of ≤2 points and no individual subscore >1 point at Week 30.

- Proportion of subjects achieving clinical response, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point, at Week 30.
- Proportion of subjects achieving clinical response (based on partial Mayo score), which is defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point at, Week 14.
- Proportion of subjects using oral corticosteroids at Baseline who have discontinued corticosteroids and are in clinical remission, at Week 30.
- Proportion of subjects achieving durable clinical response, which is defined as clinical response based on partial Mayo score at Weeks 14 and 30.

Safety Endpoints:

- Safety as assessed by adverse events (AEs), adverse events of special interest (AESIs) (including serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or injection site reactions or systemic reactions and hypersensitivity), serious adverse events (SAEs), vital signs, and results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis).

Statistical Considerations:

All efficacy analyses will be based on the full analysis set (FAS), with the exception of corticosteroid-free remission which will be based on the subset of the FAS who are taking concomitant oral corticosteroids at Baseline.

All proportion-based primary and secondary efficacy endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion by treatment group. The difference in proportions between treatment groups along with the 95% confidence interval will be presented. The primary efficacy analyses will be based on logistic model with treatment as a factor, natural logarithm of trough concentration at Week 6 and other important covariates as explanatory variables. Odds ratio and its 95% confidence interval for treatment effect will be provided All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis.

Sample Size Justification: The sample size was based on an estimate of precision and not on statistical power considerations. A total sample size of approximately 250 subjects enrolled to achieve approximately 100 subjects randomized at Week 6, including 50 subjects per treatment group, will be sufficient to provide 95% confidence intervals for mucosal healing rates with a half width no wider than +/-13.9%. In addition, the maximum width of the 95% confidence intervals (2-sided) for the difference in mucosal healing rates between the 2 groups will be no wider than +/-19.6%. If there is a high rate of patient drop out from the study, additional patients may be added.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier document. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-ASAs	5-aminosalicylates
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVA	antivedolizumab antibody
CD	Crohn's disease
CL_L	linear clearance
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
C_{trough}	observed concentration at the end of a dosing interval
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFX	infliximab
Ig	immunoglobulin

INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
JCV	John Cunningham virus
K2EDTA	potassium ethylenediamine-tetraacetic acid
LFT	liver function tests
LTFU	long-term follow-up
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MED ID	medication identification number
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
Q4W	every 4 weeks
Q8W	every 8 weeks
RAMP	Risk Assessment and Management Program for PML
RBC	red blood cell
RNA	ribonucleic acid
ROC	receiver operating characteristic
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
SVR	sustained virological response
TAXIT	Trough Level Adapted Infliximab Treatment
TB	tuberculosis
TDM	therapeutic drug monitoring
TEAE	treatment-emergent adverse events
TNF-α	tumor necrosis factor-alpha
TPN	total parenteral nutrition
TYSABRI	natalizumab
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
V_c	central compartment volume of distribution

VCAM-1	vascular cell adhesion molecule-1
WBC	white blood cell
WOCBP	woman of child bearing potential
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

3.5 Study Definitions

Term	Definition
High clearance	Week 5 serum vedolizumab concentration <50 µg/mL
Very high clearance	Week 5 serum vedolizumab concentration <30 µg/mL
Complete Mayo score	A composite index of 4 disease activity variables (stool frequency, rectal bleeding, findings on sigmoidoscopy, and physician's global assessment), each scored on a scale from 0 to 3 (higher scores indicate greater disease activity).
Partial Mayo score	A composite index of 3 disease activity variables (stool frequency, rectal bleeding, and physician's global assessment), each scored on a scale from 0 to 3 (higher scores indicate greater disease activity). Partial Mayo score is calculated analogously to the complete Mayo score but excludes the sigmoidoscopy subscore.
Clinical remission by complete Mayo score	A complete Mayo score of ≤2 points and no individual subscore >1 point.
Clinical response by complete Mayo score	A reduction in complete Mayo score of ≥3 points and ≥30% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
Clinical response by partial Mayo score	A reduction in partial Mayo score of ≥2 points and ≥25% from Baseline (Day 1) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point
Corticosteroid-free remission	Subjects using oral corticosteroids at Baseline (Day 1) who have discontinued oral corticosteroids and are in clinical remission at Week 30.
Durable clinical response	A clinical response (based on partial Mayo score), which is defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point at Weeks 14 and 30.
Mucosal healing	A Mayo endoscopic subscore of ≤1 point.
Vedolizumab IV standard dosing	Vedolizumab IV 300 mg infused intravenously at Weeks 0, 2, and 6 and then once every 8 weeks (Q8W) thereafter.
Tumor necrosis factor-alpha (TNF-α) antagonist failure categories	
Primary nonresponse	Persistently active disease despite induction treatment.
Secondary nonresponse	Recurrence of symptoms during maintenance dosing following prior clinical benefit.
Intolerance	Occurrence of treatment-related toxicities.

4.0 INTRODUCTION

4.1 Background

4.1.1 Diseases and Current Treatments

Ulcerative colitis (UC) is characterized by diffuse, superficial inflammation of the colonic mucosa that begins in the rectum and extends proximally to involve any contiguous length of the colon. The prevalence of UC is approximately 200/100,000 of the United States population and approximately 150/100,000 of the population in Western Europe [1-3] and 63.6/100,000 of the population in Japan [4]. A genetic contribution to the disease is indicated by the increased incidence of UC (of 30 to 100 times that of the general population) among first-degree relatives of patients with UC. The characteristic pathology is one of chronic inflammation characterized by large numbers of lymphocytes and histiocytes in the diseased mucosa and submucosa with an acute inflammatory infiltrate composed of neutrophils variably present.

Clinical manifestations of UC include diarrhea, typically bloody, as well as abdominal pain, fecal urgency, and incontinence. Systemic features such as fever, weight loss, malaise, and fatigue are indicators of more extensive disease. Extra-intestinal manifestations which track intestinal activity such as peripheral arthritis (type1), episcleritis, and erythema nodosum are commonly associated with inflammatory bowel disease (IBD), whereas those that manifest independent of disease activity such as ankylosing spondylitis, pyoderma gangrenosum, primary sclerosing cholangitis, and uveitis may be seen as well. The diagnosis of UC is usually made by the clinical presentation and key features of the history, physical examination, in combination with laboratory and imaging studies.

Current treatments have been effective for many patients with UC but have numerous limitations for patients with moderately to severely active disease. 5-aminosalicylates (5-ASAs) are the mainstay of UC pharmacotherapy for induction and maintenance of remission for patients with mild to moderate disease, but are less effective in moderate to severe disease [5,6].

Corticosteroids are often required for the 1/3 of patients who fail to respond to 5-ASAs [7,8]. While highly effective for induction of remission, corticosteroids are not recommended for maintenance of remission and carry significant undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection.

Immunomodulatory agents, including 6-mercaptopurine and azathioprine, have a role in maintenance of remission in moderately to severely active UC. Their relatively slow onset of action precludes their use during flares of disease, and the use of these agents has been reported to potentially increase the risk of lymphoma in patients with IBD [9]. Other severe adverse events (AEs) associated with use of immunomodulators include cytopenias, hepatitis, and infection.

Intravenous (IV) cyclosporine has a role in the management of severely active UC; however, it is impractical in non-hospitalized patients, requires intense monitoring, and may cause irreversible nephrotoxicity, all of which limit its use.

Monoclonal antibodies (mAbs) directed against tumor necrosis factor-alpha (TNF-α) have been approved for the treatment of UC in many countries world-wide, including infliximab (Remicade), adalimumab (Humira) and golimumab (Simponi) [10-12]. These agents have substantially improved the care of patients with UC by inducing and maintaining remission and decreasing the need for hospitalizations and surgeries, and other complications. Although TNF-α antagonists represent an important addition to the UC pharmacologic armamentarium, they are effective in only a subset of patients, with roughly 2/3 of patients in controlled trials not in remission at the end of the first year of therapy [13,14]. Induction of remission with infliximab occurs in only 31% to 39% of patients with UC [15] and durable clinical remission (ie, defined as clinical remission at Weeks 8, 30, and 54) occurs in only 26% of patients with UC. In addition, controlled studies have demonstrated that, after failure of 1 TNF-α antagonist, a patient's response to a second TNF-α antagonist is substantially lower [16]. The TNF-α antagonists are also associated with a number of serious safety concerns based on their suppression of systemic immunity, including reactivation of tuberculosis (TB); various bacterial, viral, fungal, and opportunistic infections; and malignancies, such as hepatosplenic T cell lymphoma [10,11].

Failure of pharmacological therapy leads to colectomy in 9% to 35% of patients with UC within 5 years. Colectomy is considered to be an important adjunct treatment for refractory UC; however, colectomy with ileal pouch anal anastomosis (the standard surgical therapy) has many limitations and is associated with its own set of complications, including high stool frequency [17], female infertility [18], and a cumulative incidence of pouchitis of 50% at 10 years [19]. The limitations of current therapies for UC indicate that there is a significant need for safer and more effective therapies.

4.1.2 Vedolizumab IV

Vedolizumab (also known as MLN0002) is a novel recombinant humanized mAb composed of 2 light chains of the κ subclass and 2 immunoglobulin (Ig) G_1 heavy chains. Vedolizumab binds specifically to the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$integrin mediates lymphocyte trafficking to gastrointestinal (GI) mucosa and gut-associated lymphoid tissue (GALT) through adhesive interaction with mucosal addressin cell adhesion molecule-1 **(**MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [20-23]. As a result, vedolizumab impairs the migration of gut-homing leukocytes into GI mucosa [24] and acts as a gut-selective immunomodulator.

Vedolizumab IV (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; or MLN0002 IV) has been granted marketing approval in numerous regions, including the United States (US), Canada, and European Union (EU). Vedolizumab IV is approved for the treatment of adult patients with moderately to severely active UC and CD, who have failed conventional treatment, such as immunomodulators, corticosteroids, or TNF-α antagonists. The approved dosing and administration regimen is 300 mg vedolizumab IV infused intravenously at Weeks 0, 2, and 6 and then every 8 weeks (Q8W) thereafter and is the standard vedolizumab dosing regimen referred to in this protocol.

Previously conducted clinical studies have characterized the efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of vedolizumab IV, a lyophilized formulation. As of 19 May 2015, approximately 3600 subjects (309 healthy subjects, 1393 subjects with UC, and 1896 subjects with Crohn's disease [CD]) have received at least 1 dose of vedolizumab across completed and ongoing studies (Edition 18 of Investigator's Brochure). Vedolizumab exposure has extended for ≥12 months in 1667 subjects, ≥24 months in 1306 subjects, ≥36 months in 935 subjects, ≥48 months in 676 subjects, ≥60 months in 267 subjects, and ≥72 months in 26 subjects. Based on drug shipment data (19 November 2015), the cumulative patient exposure to vedolizumab IV since its marketing approval in May 2014 is estimated to be approximately 25,831 patient-years.

In subjects with moderately to severely active UC (Study C13006), vedolizumab IV 300 mg administered as an IV infusion at Weeks 0 and 2 (induction) followed by either once every 4 weeks (Q4W) or Q8W administration from Week 6 through Week 52 (maintenance) induced a statistically-significant increase in rates of clinical response at Week 6 and clinical remission at Week 52 (primary endpoint for the Induction Period and Maintenance Period, respectively) compared with placebo [25]. The study also met important secondary endpoints, including durable clinical response, durable clinical remission, mucosal healing at Weeks 6 and 52, and corticosteroid-free clinical remission at Week 52. Given the significant morbidity associated with chronic corticosteroid treatment, the corticosteroid-sparing effects of vedolizumab provide an important benefit to patients with UC.

Vedolizumab IV has shown an acceptable and consistent safety profile in clinical studies and postmarketing. In the pivotal phase 3 studies (C13006 in UC and C13007 in CD), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (SAEs) have been related to exacerbations or complications of the underlying UC or CD. For those infections that were reported more frequently in vedolizumab-treated subjects, the sites of these infections correlated with the known tissue distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). A total of 4% of vedolizumab-treated subjects and 3% of placebo-treated subjects experienced an infusion-related reaction. In C13006 and C13007, 10% of subjects were positive for antivedolizumab antibodies (AVA) 16 weeks following the last dose of vedolizumab IV. Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment.

A similar safety profile was observed in subjects who received vedolizumab IV Q4W or Q8W. Overall, the safety profile following long-term treatment with vedolizumab in C13008, a long-term safety study, is consistent with safety in the completed studies. No cases of progressive multifocal leukoencephalopathy (PML) have been identified to date in the clinical or postmarketing setting.

Vedolizumab PK is described by a 2-compartment model with parallel linear and nonlinear elimination. Using reference covariate values, the linear elimination half-life of vedolizumab is 25.5 days; linear clearance (CL_L) is 0.159 L/day for UC and 0.155 L/day for CD; central compartment volume of distribution (V_c) is 3.19 L; and peripheral compartment volume of distribution is 1.66 L. Only extreme albumin and body weight values have been identified as potential clinically important predictors of vedolizumab CL_L [26].

As higher therapeutic mAb concentrations have been associated with greater efficacy in patients with UC or CD, a better understanding of the determinants of vedolizumab clearance may help to optimize dosing [27].

4.2 Rationale for the Proposed Study

Medical management of UC, along with that of other chronic diseases, is evolving toward a personalized treatment approach. Therapeutic drug monitoring (TDM), the observed concentration at the end of a dosing interval (C_{trough}) with dosing titration to achieve a prespecified therapeutic range, is one modality that is increasingly employed to enhance UC patient care [28].

Approximately 1/3 of patients fail to respond to induction therapy of TNF-α antagonists and up to 60% experience secondary loss of response. Differences in drug clearance may be an important explanation for this observation. Patients who lose response are typically managed empirically by dose intensification, switching to another agent with the same mechanism of action, or moving to an agent with a different mechanism of action. With a limited number of therapeutic options available, health care providers are optimizing the use of TNF-α antagonists by taking advantage of TDM [27,29].

Several factors are associated with accelerated clearance of monoclonal antibodies, including the presence of anti-drug antibodies, sex, body size, concomitant immunosuppressant use, IBD type, albumin concentration, and degree of systemic inflammation [26]. Furthermore, a consistent relationship between efficacy and exposure, in distinction to drug dose, has been observed for many of these agents; that is, higher C_{trough} values are associated with greater efficacy [30].

Recent studies suggest a correlation between serum drug concentrations and clinical outcomes such as clinical and endoscopic remission [27]. Very few prospective clinical studies that compare the optimal therapeutic ranges and clinical outcomes for biologic therapies for UC and CD (ie, TNF-α antagonists) have been conducted to date. The Trough Level Adapted Infliximab Treatment trial (TAXIT) was a randomized controlled trial of 251 UC and CD patients that dose optimized all patients into a therapeutic window and then compared patients dosed by drug concentration dosing versus clinically based dosing for infliximab (IFX) maintenance therapy. After dose optimization, continued concentration-based dosing was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment [29].

A similar understanding of the optimal therapeutic target range for vedolizumab IV is particularly important given its mechanism of action. Data for multiple endpoints from the vedolizumab IV UC clinical studies [25,31] were analyzed to gain insight into the exposure-response relationships for

vedolizumab IV. During UC induction therapy at Week 6 in Study C13006, there was a strong relationship between vedolizumab C_{trough} levels and clinical remission. In addition, endoscopic subscores were improved and mucosal healing was more common among subjects who had higher vedolizumab C_{trough} levels at Weeks 6 and 46. Week 6 vedolizumab C_{trough} levels for subjects with the highest endoscopic subscores were below the overall Week 6 median C_{trough} levels in C13006 [26,32]. From this analysis at Week 6 (end of induction), patients with an endoscopic subscore of 3 had on average 25% higher CL_L, than patients with an endoscopic subscore of 0 [26].

In the C13006 UC study, 47% of subjects achieved clinical response at Week 6 [25]. Of those subjects who failed to respond, 89% had vedolizumab C_{trough} levels <40 µg/mL, which may partly be attributed to high drug clearance. Clearance is the most important PK parameter for determination of dose. Individuals with vedolizumab clearance >0.14 L/day were associated with diminished efficacy outcomes. Improved outcomes may be seen by the administration of higher induction doses resulting in greater serum concentrations. Given the clearance cut-point of 0.14 L/day and the approved vedolizumab IV dosing regimen, a target steady state vedolizumab trough concentration >12.7 µg/mL was calculated. Simulations with the published population PK model were conducted to evaluate strategies to (1) identify high clearance individuals, and (2) recommend dose adjustments necessary to achieve the steady-state target, both based on Week 5 plasma vedolizumab concentrations in this study.

Additional support for this hypothesis is provided by the results from a small, prospective study with vedolizumab IV conducted in IBD patients (N=34) who failed 2 lines of TNF-α antagonist therapy [33]. Results from this study support the value of an early assessment of vedolizumab concentrations to predict whether dose-optimization is needed following administration of vedolizumab IV 300 mg on Day 1 and Weeks 2 and 6. A predictive threshold for sustained remission at Week 6 was analyzed using a receiver operating characteristic (ROC) curve (area under the curve: 0.84). A cut-off for vedolizumab (37 µg/mL) at Week 6 was predictive of sustained remission with a sensitivity of 100% and a specificity of 70%. Moreover, a cut-off for vedolizumab (41 µg/mL) at Week 6 was predictive of nonoptimization at Week 10, with a sensitivity of 75% and a specificity of 100%.

This phase 4, prospective, open label, multi-center clinical study in adult subjects with moderately to severely active UC is being performed to evaluate the efficacy and safety of vedolizumab IV dose optimization, compared with standard dosing, in Week 6 nonresponders identified as having high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL). This study will evaluate the potential benefit of vedolizumab IV dose optimization on patient outcomes based on the derived target C_{trough} levels.

4.3 Benefit-Risk Assessment

The proposed Vedolizumab–4014 study is designed to evaluate the effect of vedolizumab IV dose optimization on mucosal healing compared with the standard vedolizumab IV dosing at Week 30. The target population consists of patients who have moderately to severely active UC who have had an inadequate response to prior therapy (consistent with the approved vedolizumab IV label) and who have not responded to standard vedolizumab induction therapy at Week 6 and have high

vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL). Clinical outcomes for the standard vedolizumab dosing regimen will be compared with the dose-optimized regimens.

An unmet need exists for patients who do not respond to UC therapy. Fifty-three percent of subjects did not achieve clinical response at Week 6 in the C13006 study with vedolizumab IV. Higher doses are projected to produce exposure levels that have been safely studied in previous clinical studies and may result in efficacy in subjects who have high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL). In addition, if C_{trough} levels exceed the exposure limit of 90 µg/mL, protocol instructions are designed to decrease subsequent doses and decrease exposure.

Overall, vedolizumab IV has been well tolerated in clinical studies and the benefit-risk profile is positive for the defined study population.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

To determine the effect of vedolizumab IV dose optimization on mucosal healing compared with the standard vedolizumab IV dosing regimen at Week 30 in subjects with UC and high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL) and who are Week 6 nonresponders.

5.1.2 Secondary Objectives

To determine the effect of vedolizumab IV dose optimization on clinical response and remission compared with the standard vedolizumab IV dosing regimen at Week 30 in subjects with UC and high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL) and who are Week 6 nonresponders.

5.1.3 Additional Objectives

Safety Objective:

- To evaluate the safety of administering higher induction doses of vedolizumab IV compared with the standard dosing regimen over the 30-week treatment period in subjects with UC and high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL) and who are Week 6 nonresponders.

Additional Objectives:

- Additional proteomic or cellular biomarker analyses that correlate with response may be performed in the future and reported separately.

5.2 Endpoints

5.2.1 Primary Endpoint

Proportion of subjects achieving mucosal healing (defined as Mayo endoscopic subscore ≤1 point) at Week 30.

5.2.2 Secondary Endpoints

- Proportion of subjects achieving clinical remission, where clinical remission is defined as a complete Mayo score of ≤2 points and no individual subscore >1 point at Week 30.
- Proportion of subjects achieving clinical response, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point, at Week 30.

- Proportion of subjects achieving clinical response (based on partial Mayo score), which is defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point, at Week 14.
- Proportion of subjects using oral corticosteroids at Baseline who have discontinued corticosteroids and are in clinical remission, at Week 30.
- Proportion of subjects achieving durable clinical response, which is defined as clinical response based on partial Mayo score at Weeks 14 and 30.

5.2.3 Additional Endpoints

- Change in C-reactive protein (CRP) levels from Baseline to Week 6, 14, and 30.
- Change in fecal calprotectin concentrations from Baseline to Weeks 6, 14, and 30.
- Proportion of subjects with positive AVAs and positive neutralizing AVAs.
- Proportion of subjects with C_{trough} values that fall below the threshold targets of 18.4 µg/mL at Week 14 and 12.7 µg/mL at Week 30.
- Change from Baseline to Week 30 in health-related quality of life (HRQOL) based on inflammatory bowel disease questionnaire (IBDQ) scores.
- Proportion of subjects achieving a stool frequency subscore = 0; rectal bleeding subscore = 0 and endoscopy subscore = 0 or 1 (modified so that a score of 1 does not include friability).
- Proportion of subjects achieving a stool frequency subscore = 0 or 1 and a prespecified specific change of 1 or more from Baseline and rectal bleeding subscore = 0; and endoscopy subscore = 0 or 1 (modified so that a score of 1 does not include friability).

Safety Endpoint

- Safety as assessed by AEs, adverse events of special interest (AESIs) (including serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or injection site reactions or systemic reactions and hypersensitivity), SAEs, vital signs, and results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 4, open-label, multicenter study to investigate the efficacy and safety of dose optimization of vedolizumab IV, compared with standard dosing of vedolizumab IV, over a 30-week treatment period (ie, a 6-week Lead in Period followed by 24-week Randomized Treatment Period). This study will enroll adult subjects with moderately to severely active UC who are eligible for treatment with vedolizumab IV. Approximately 250 subjects will be enrolled in order to randomize approximately 100 nonresponder subjects with high vedolizumab drug clearance.

The study is comprised of a 28-day Screening Period, a 6-week Lead-in Period, and a 24-week Randomized Treatment Period, followed by an 18-week Follow-up visit and a long-term follow-up (LTFU) safety survey by telephone at 6 months after the last dose of study medication. The study visits schedule and assessments will be completed per the schedule of study procedures in Appendix A. A schematic of the study design is included in Figure 6.a.

On Day 1 and Week 2 (Lead-in Period), all eligible subjects will receive vedolizumab IV 300 mg. At Week 5, serum vedolizumab concentration will be measured. At Week 6, subjects will be assessed for clinical response based on partial Mayo score (see definition of complete response by partial Mayo score in Section 3.5 Study Definitions).

Results of both Week 5 vedolizumab concentration and Week 6 clinical response will establish which of the following 2 treatment pathways a subject will follow at Week 6:

- Pathway 1: Subjects who are nonresponders based on partial Mayo score at Week 6 and who are assessed as having high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL) will proceed with randomization at Week 6 in a 1:1 ratio to receive either dose-optimized or standard vedolizumab IV therapy as described below.
- Pathway 2: Subjects who respond at Week 6 or have levels above a predefined Week 5 serum vedolizumab concentration threshold (≥50 µg/mL) (Lead-in Failure) will not be randomized and will receive the Week 6 study dose (300 mg) and thereafter appropriate treatment per physician discretion. Following the last dose of study drug (Week 6), subjects will have the 18-week Follow-Up Safety Visit and 6 month LTFU phone call.

At Week 6, eligible subjects will be randomized 1:1 into the Standard Treatment arm or the Dose Optimized arm (ie, Pathway 1), stratified by TNF-antagonist naïve or failure status and receive the following treatments:

- Vedolizumab IV Standard Treatment Arm:

  Vedolizumab IV 300 mg Q8W (Weeks 6, 14, and 22).

- Vedolizumab IV Dose Optimized Arm:

  Week 6: Dose Assignments for Dose Optimization Arm

  At Week 6, all subjects randomized to the Dose Optimization Arm will be assigned to either Regimen A or Regimen B (below) based on the subject's Week 5 serum vedolizumab concentration. Subjects with serum vedolizumab concentration <50 µg/mL and ≥30 µg/mL will be assigned to Regimen A, and subjects with serum vedolizumab concentration <30 µg/mL will be assigned to Regimen B:

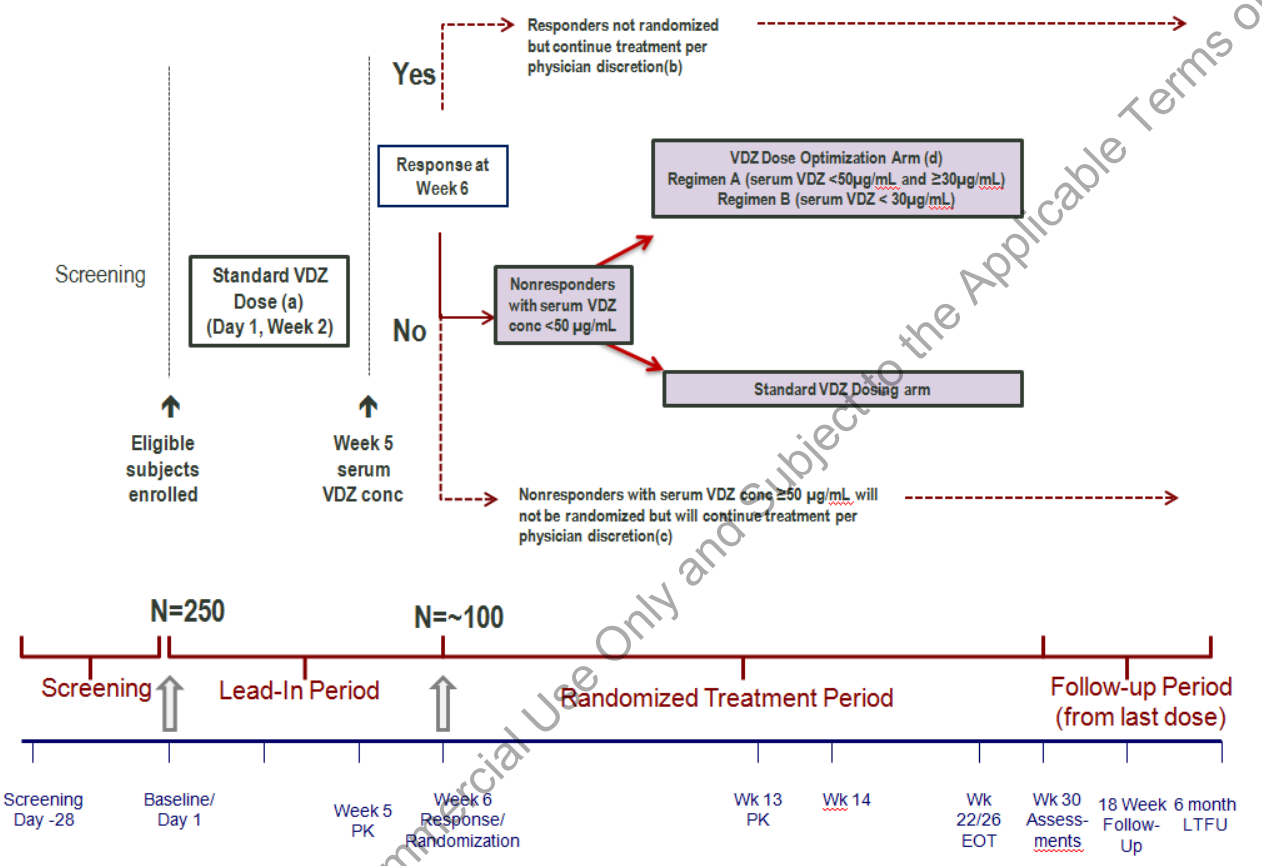
  Regimen A: Vedolizumab IV 600 mg (Week 6) and 300 mg Q4W (Weeks 10, 14, 18, 22, and 26), OR
  Regimen B: Vedolizumab IV 600 mg (Week 6) and 600 mg Q4W (Weeks 10, 14, 18, 22, and 26)

  Week 14: Dose Optimization Arm

  At Week 14 and beyond, dosing will continue as previously scheduled unless the subject's most recent preceding serum vedolizumab concentration is >90 µg/mL (eg, Week 13 PK sampling prior to Week 14 dosing). In the event that steady-state C_{trough} levels exceed safety exposure limits of 90 µg/mL, the next dose will be withheld and another PK sample will be taken 1 week prior to the next scheduled dose. If at the next scheduled dose the C_{trough} is still >90 µg/mL, the next dose will be similarly held and the PK repeated 1 week prior to the next scheduled dose. Once C_{trough} is ≤90 µg/mL, the subject will move to the next lowest dose. For example

  If subject was on 300 mg Q4W, then subject goes to next lower dose or 300 mg Q8W dose.
  If subject was on 600 mg Q4W, then subject goes to next lower dose or 300 mg Q4W dose.
  If subject was moved from 600 mg Q4W to 300 mg Q4W and subsequent C_{trough} >90 µg/mL, then subject goes to next lowest dose (ie, 300 mg Q8W).

Figure 6.a Schematic of Study Design



Conc=concentration, EOT=end of treatment, VDZ=vedolizumab.
(a) On Day 1 and Week 2 (Lead-in Period), all eligible subjects will receive vedolizumab IV 300 mg.
(b) Subjects who respond at Week 6 (by partial Mayo score) will not be randomized and will receive the Week 6 study drug dose and thereafter receive appropriate treatment per physician discretion. Following the last dose of study drug (Week 6), subjects will have the 18-week Follow-Up Safety Visit and 6 month LTFU telephone call.
(c) Subjects who are nonresponders at Week 6 and have levels above a predefined serum vedolizumab concentration threshold (≥50 µg/mL) at Week 5 (Lead-in Failures), will not be randomized and will receive the Week 6 study drug dose and thereafter receive appropriate treatment per physician discretion. Following the last dose of study drug (Week 6), subjects will have the 18-week Follow-Up Safety Visit and 6 month LTFU telephone call.
(d) At Week 14 and beyond, dosing will continue as previously scheduled unless the subject's most recent preceding serum vedolizumab concentration is >90 µg/mL. The dose will be withheld and PK will be repeated 1 week prior to the next scheduled dose until C_{trough} is ≤90 µg/mL. Once ≤90 µg/mL, the subject will move to the next lower dose.

6.2 Justification for Study Design, Dose, and Endpoints

This phase 4, prospective, open label, multicenter trial in adult patients with moderately to severely active UC is designed to evaluate the efficacy and safety of vedolizumab IV dose optimization, compared with the standard vedolizumab dosing regimen, in Week 6 nonresponders

identified as having high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL). This study will evaluate the potential benefit of vedolizumab IV dose optimization on clinical outcomes based on derived target C_{trough} levels.

Vedolizumab doses ranging from 0.2 to 10 mg/kg and 180 to 750 mg in healthy subjects and in subjects with UC or CD have been tested in clinical studies. The highest exposures following multiple dose administration of vedolizumab IV were observed in the phase 2 study C13002 in subjects with UC [31]. In C13002, individual C_{trough} levels ranged from 13.4 to 155 µg/mL at Day 85 following administration of 10 mg/kg vedolizumab IV at Weeks 0, 2, 4, and 12; the highest exposure was observed in a 95 kg subject weighing who received 900 mg of vedolizumab IV for each infusion. Safety in this study was consistent with the overall safety profile observed with vedolizumab IV. The median C_{trough} concentration in this phase 2 study was 90 µg/mL, which was selected as the safe exposure limit for the current study.

Phase 2 and 3 data from the vedolizumab clinical studies contributed to the population PK model that was used to simulate the estimated C_{trough} following administration of vedolizumab IV 600 mg Q4W (the maximum dose to be administered in this study) in subjects with high clearance [26]. Based on simulations of Week 5 plasma vedolizumab concentrations, strategies to 1) identify high clearance subjects (eg, clearance >0.14 L/day), and 2) recommend dose adjustments were explored. Results revealed that a Week 5 plasma vedolizumab concentration <50 µg/mL cut point would capture most of the high-clearance subjects while minimizing the fraction of lower-clearance subjects who might be misclassified. A dosing strategy was selected that would result in a higher proportion of subjects achieving C_{trough} concentrations >12.7 µg/mL at steady-state and be within the range of concentrations found to be safe in clinical studies, ensuring virtually no subjects would be expected to exceed the maximum trough concentration of 90 µg/mL. The following 2 regimens were selected to begin at Week 6 based on Week 5 vedolizumab concentrations: Regimen A for subjects with Week 5 vedolizumab concentration of ≥30 µg/mL but <50 µg/mL, and Regimen B for subjects with Week 5 vedolizumab concentrations of <30 µg/mL.

The approved dosing regimen of vedolizumab IV 300 mg at Weeks 0, 2, 6, and then Q8W thereafter (through Week 22) will be tested in the Standard Dosing Arm. For all subjects randomized to the Dose Optimized Arm, vedolizumab IV 600 mg at Week 6 followed by either 300 mg Q4W or 600 mg Q4W (through Week 26) will be tested. The assessment of target concentrations and high clearance was based on phase 3 GEMINI data [25], which identified a maximum dose of 600 mg to account for the variability of clearance among subjects. The maintenance dosing interval Q4W is necessary to achieve the derived target concentration in the highest clearance individuals evidenced by a Week 5 serum vedolizumab concentration <30 µg/mL. Subjects with Week 5 serum vedolizumab concentrations above or equal to 30 µg/mL and below 50 µg/mL will receive maintenance doses of 300 mg Q4W in order to achieve the steady state serum vedolizumab target concentration.

The primary endpoint is the proportion of subjects achieving mucosal healing (defined as Mayo endoscopic subscore ≤1 point) at Week 30. Assessment at Week 30, or 6 months from the Week 6 randomization, was selected as it's a real-world time point for mucosal healing (Ulcerative Colitis

and Crohn's Disease: Outcomes From the VICTORY Consortium) [34]. The presence of mucosal healing has been demonstrated to decrease the risk of relapse, hospitalizations, colorectal cancer, and colectomy. Endoscopic assessment has been demonstrated to be a feasible and more beneficial strategy than clinical assessment to guide treatment optimization in UC patients. Although different endoscopic scores have been used to define mucosal healing, the Mayo endoscopic subscore 0 or 1 has been one of the most used definitions. Endoscopies will be read by a central reader to eliminate interpretation bias and allow the study to remain open label for subject convenience. Additional efficacy assessments are included as part of the secondary endpoints of the study.

The Week 6 time point for assigning dosing regimens was selected based upon the correlation of C_{trough} concentrations at Week 6 with clinical remission status at Week 14 [25]. The Week 14 time point, which is an established efficacy evaluation time point for vedolizumab, was designed as a check to allow for dose reduction from the initial dosing regimen in the event that the Week 13 serum vedolizumab concentration exceeded 90 µg/mL since approximately 75% of the steady-state exposure will be achieved at that time.

FcRn receptor gene polymorphisms may impact vedolizumab drug clearance and, as a result, influence clinical outcomes. Pharmacogenomic analysis may be conducted to investigate the contribution of genetic variance on drug clearance in subjects identified as having a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL).

Participation of study subjects in pharmacogenomics (PGx) sample collection is optional, and subjects will have the capability to opt in to the PGx informed consent. As PGx is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, must be confirmed prior to enrollment at Baseline/Day 1.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry on Day 1 into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is male or female and between age 18 to 85 years, inclusive, at Screening.
4. The subject has a diagnosis of UC established at least 1 month prior to Screening by clinical and endoscopic evidence and corroborated by a histopathology report.
5. The subject has moderately to severely active UC as determined by a complete Mayo score of 6 to 12 with an endoscopic subscore ≥2 within 28 days prior to enrollment.
6. The subject has evidence of UC proximal to the rectum (≥15 cm of involved colon) prior to start of vedolizumab IV dosing.
7. The subject has been determined to be suitable for vedolizumab IV for routine management of UC by their physician.
8. The subject with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance (may be performed during screening).
9. The subject has had an inadequate response with, lost response to, or intolerance of at least 1 of the following agents: immunomodulators, corticosteroids, or TNF-α antagonists. Subjects who are naïve to TNF-α antagonist therapy or who have previously failed TNF-α antagonist therapy (including primary and secondary nonresponders or intolerant) may be included.
10. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with or without spermicide)* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose. The female partner of a male subject should also be advised to use a highly effective/effective method of contraception.*
11. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective/effective method of contraception* from signing of informed consent throughout the duration of the study and 18 weeks after the last dose.

*Definitions and highly effective methods of contraception are defined in Section 9.1.14 and reporting responsibilities are defined in Section 9.1.15.

7.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study.

1. The subject has clinical evidence of abdominal abscess or toxic megacolon at the Screening Visit.
2. The subject has had an extensive colonic resection, subtotal or total colectomy.
3. The subject has had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
4. The subject has a diagnosis of Crohn's colitis or indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis.
5. The subject has received any of the following for the treatment of underlying disease within 30 days of screening:
   a) Non-biologic therapies (eg. cyclosporine, tacrolimus, thalidomide) other than those specifically listed in Section 7.4.2 Permitted Medications For Treatment of UC.
   b) An approved non-biologic therapy in an investigational protocol.
6. The subject has received any investigational or approved biologic or biosimilar agent within 60 days or 5 half lives prior to screening (whichever is longer).
7. The subject has had prior exposure to approved or investigational anti-integrin antibodies (eg, natalizumab, efalizumab, etrolizumab, AMG-181, anti-MAdCAM-1 antibodies, or rituximab).
8. The subject has previously received approved or investigational vedolizumab.
9. The subject currently requires or is anticipated to require surgical intervention for UC during the study.
10. The subject has history or evidence of adenomatous colonic polyps that have not been removed, or colonic mucosal dysplasia.
11. The subject has any evidence of an active infection during Screening (eg, sepsis, cytomegalovirus, or listeriosis).
12. The subject has a clinically significant infection (eg, pneumonia, pyelonephritis) within 30 days prior to screening, or ongoing chronic infection.
13. The subject has evidence of active *C. difficile* as evidenced by positive *C. difficile* toxin or is having treatment for *C. difficile* infection or other intestinal pathogens during Screening.
14. The subject has a known history of infection with human immunodeficiency virus (HIV), hepatitis B (HBV)*, or chronic HBV or hepatitis C virus (HCV) infection. Subjects with documented successful treatment of HCV with sustained virological response (SVR) at 26 weeks can be enrolled.
    * HBV immune subjects (ie, being hepatitis B surface antigen [HBsAg] negative and hepatitis B antibody positive) may, however, be included.

15. The subject has active or latent TB as evidenced by the following:
    a) A diagnostic TB test performed within 30 days of Screening or during the Screening Period that is positive, defined as:
        1. Positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, OR
        2. A TB skin test reaction ≥5 mm.
           NOTE: If subjects have received BCG vaccine then a QuantiFERON TB Gold test should be performed instead of the TB skin test.

    OR

    b) Chest X-ray within 3 months of Screening that is suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON tests within 30 days prior to Screening or during the Screening Period.
       Note: subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study.
16. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, HIV infection, organ transplantation).
17. The subject has any live vaccination within 30 days prior to Screening or is planning to receive any live vaccination during participation in the study.
18. The subject has used a topical (rectal) treatment with (5-ASA) or corticosteroid enemas/suppositories within 2 weeks prior to Screening.
19. The subject has a history of hypersensitivity or allergies to vedolizumab IV or its components.
20. The subject has received total parenteral nutrition (TPN) or albumin in the last 30 days prior to Screening.
21. The subject has any unstable or uncontrolled cardiovascular disorder, heart failure moderate to severe (New York Class Association III or IV), any pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
22. The subject has had a surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.
23. The subject has a history of malignancy, except for the following: adequately-treated nonmetastatic basal cell skin cancer; squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to Screening; and history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to screening. Subject with remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case by-case basis prior to Screening.

24. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease.
25. The subject has a positive PML subjective symptom checklist during Screening or prior to the administration of the first dose of study drug on Day 1.
26. Any of the following laboratory abnormalities during the Screening period:
    a) Hemoglobin level <8 g/dL.
    b) White blood cell (WBC) count $<3\times10^9$/L.
    c) Lymphocyte count $<0.5\times10^9$/L.
    d) Platelet count $<100\times10^9$/L or $>1200\times10^9$/L.
    e) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× the upper limit of normal (ULN).
    f) Alkaline phosphatase >3×ULN.
    g) Serum creatinine >2×ULN.
27. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit.
28. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
29. The subject is unable to attend all the study visits or comply with study procedures.
30. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after last dose; or intending to donate ova during such time period.
31. If male, the subject intends to donate sperm during the course of this study or for 18 weeks after last dose.
32. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

7.3 Week 6 Randomized Treatment Period Inclusion Criteria

At Week 6, subjects must meet both of the following inclusion criteria to be eligible for randomization into the Randomized Treatment Period of the study:

1. Following Lead-in Period, the subject is assessed as having a high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL).
2. Following Lead-in Period, the subject is a nonresponder based on partial Mayo score at Week 6.

7.4 Excluded Medications, Procedures, and Treatments

7.4.1 Excluded Medications

The following medications are excluded from use during the study from the time of Screening through the Final Visit/ET (Week 30), unless specified otherwise:

1. Any approved or nonapproved biologic or biosimilar agent for the treatment of IBD.
2. Any approved or nonapproved nonbiologic therapy for treatment of UC in an investigational protocol.
3. Any nonbiologic therapies (eg. cyclosporine, thalidomide) for the treatment of UC other than those listed in section 7.4.2.
4. Any live vaccines through 6 months after the last dose of study drug.
5. Any approved or nonapproved biologic for the treatment of non-IBD conditions other than localized injections (eg. Intra-ocular injections for wet macular degeneration).
6. Topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories.
7. TPN or albumin.

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

7.4.2 Permitted Medications

The following medications for UC are permitted during the study:

- Probiotics (eg, Culturelle, *Saccharomyces boulardii*) provided that the subject was receiving them at the Screening Visit and they remain stable throughout the study.
- Oral 5-ASA compounds provided that the subject was receiving them at the Screening Visit and that they remain stable throughout the study.
- Oral corticosteroid therapy for UC total of up to 30 mg/day is permitted during Screening and upon enrollment. Tapering must be made at the investigator's discretion no later than Week 14. See Section 7.4.2.1.
- Antidiarrheals for control of chronic diarrhea.
- Azathioprine, 6-mercaptopurine, or methotrexate, provided that the dose has been stable for 8 weeks immediately prior to Screening and remain stable throughout the duration of the study.

7.4.2.1 Corticosteroid Taper

The maximum dose of oral prednisone for the treatment of UC that may be coadministered with vedolizumab IV is 30 mg/day or 9 mg/day budesonide (or equivalent). Oral corticosteroid taper should be initiated by Week 10 and no later than Week 14 according to the following schedule:

- For prednisone doses >10 mg/day (or equivalent), the dose will be reduced at a rate of 5 mg/week until a 10 mg/day dose is reached.
- For prednisone doses ≤10 mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) is reached, the dose will be reduced at a rate of 2.5 mg/week until discontinuation. For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids could be increased up to, but not exceed, the original dose the subject was on at the start of the induction phase. In such cases, the tapering regimen above will be reinitiated within 2 weeks.
- Budesonide should be reduced 3 mg every 2 weeks until discontinuation.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or permanent discontinuation of study medication should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.24.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
    - Liver Function Test Abnormalities

      Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.11), if the following circumstances occur at any time during study medication treatment:
      - ALT or AST >8 × ULN, or
      - ALT or AST >5 × ULN and persists for more than 2 weeks, or
      - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
      - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
2. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.15.
7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Other.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit, Final Safety Visit, and the LTFU survey.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV 300 mg

The sponsor will supply the study sites with the following study medication in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study medication will be provided in a glass vial as a lyophilized solid for reconstitution using 4.8 mL of sterile water for injection. Each vial will be packaged in an appropriately labeled single vial carton.

Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.1.2 Vedolizumab IV 600 mg

The sponsor will supply the study sites with the following study medication in an open-label manner: 2 vials of vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. Study medication will be provided in a glass vial as a lyophilized solid. Each glass vial should be reconstituted using 4.8 mL of sterile water for injection. See pharmacy manual for further instructions. Each vial will be packaged in an appropriately labeled single vial carton.

Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.2 Storage

Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

Vedolizumab IV must be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

The dose and regimen are provided in Table 8.a. Instructions for reconstitution and administration will be provided in the pharmacy manual.

Table 8.a Vedolizumab IV Dose and Regimens

Period / Decision Visit Group	Dose and Regimen	Dosing Schedule
Lead-in Period		
Day 1 and Week 2		
All subjects	Vedolizumab IV 300 mg	Day 1 and Week 2
Lead-in failure subjects will receive the Week 6 study drug dose and thereafter appropriately treated per physician discretion		
Randomized Treatment Period (a)		
Standard Therapy Arm	Vedolizumab IV 300 mg Q8W	Weeks 6, 14, 22
Dose Optimization Arm		
Week 6 Dose Assignments for Dose Optimization Arm (b)		
At Week 6, all subjects randomized to the Dose Optimization Arm will be assigned to either Regimen A or Regimen B (below) based on the subject's Week 5 serum vedolizumab concentration. Subjects with serum vedolizumab concentration <50 µg/mL and ≥30 µg/mL will be assigned to Regimen A, and subjects with serum vedolizumab concentration <30 µg/mL will be assigned to Regimen B:		
Regimen A: Vedolizumab IV 600 mg (Week 6) and 300 mg Q4W (Weeks 10, 14, 18, 22, 26), OR Regimen B: Vedolizumab IV 600 mg (Week 6) and 600 mg Q4W (Weeks 10, 14, 18, 22, 26)		
Week 14: Dose Optimization Arm Safety Checkpoint		
At Week 14 and beyond, dosing will continue as previously scheduled unless the subject's most recent preceding serum vedolizumab is >90 µg/mL (eg, Week 13 PK sampling prior to Week 14 dosing). In the event that steady-state C_{trough} levels exceed safety exposure limits of 90 µg/mL, the next dose will be withheld and another PK sample will be taken 1 week prior to the next scheduled dose. If at the next scheduled dose the C_{trough} is still >90 µg/mL, the next dose will be similarly held and the PK repeated 1 week prior to the next scheduled dose. Once C_{trough} is ≤90 µg/mL, the subject will move to the next lowest dose. For example: If subject was on 300 mg Q4W, then subject goes to next lower dose or 300 mg Q8W dose. If subject was on 600 mg Q4W, then subject goes to next lower dose or 300 mg Q4W dose. If subject was moved from 600 mg Q4W to 300 mg Q4W and subsequent C_{trough} >90 µg/mL, then subject goes to next lowest dose (ie, 300 mg Q8W).		

(a) Subjects will be randomized in a 1:1 ratio to receive either dose-optimized or standard vedolizumab IV therapy.
(b) Sites will use IRT to obtain the dose to be administered based on Week 5 serum vedolizumab concentration.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the Schedule of Study Procedures (Appendix A).

The investigator or investigator's designee will access the interactive response technology (IRT) at Screening to obtain the subject study number.

At Day 1 and Week 2, the investigator or the investigator's designee will use the IRT to dispense the subject's study drug. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. The medication identification number (Med ID) of the study drug to be dispensed will then be provided by the IRT by email notification to the site pharmacist/nurse. If sponsor-supplied study drug is lost or damaged, the site staff can request a replacement from the IRT.

For subjects that are lead-in failures at Week 6, the IRT will dispense 300 mg vedolizumab if requested per physician discretion.

At Week 6, the investigator or the investigator's designee will use the IRT to randomize the subject into the Randomized Treatment Period of the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening and Week 5 vedolizumab serum concentration. The subject will be randomized into 1 of 2 treatment arms, the Standard Dosing or the Dose Optimized arm. For subjects randomized to the Dose Optimization Arm, dosing regimens will be assigned by the IRT based on the Week 5 serum vedolizumab concentration. The Med ID of the study drug to be dispensed will then be provided by the IRT by email notification to the site pharmacist/nurse. If sponsor-supplied study drug is lost or damaged, the site staff can request a replacement from the IRT.

At Week 14 and beyond, for subjects in the Dose Optimization Arm, the investigator or the investigator's designee will enter the subject's most recent preceding serum vedolizumab concentration into IRT prior to dosing. If serum vedolizumab is >90 µg/mL, the next dose will be withheld and subject will be brought back the week before the next scheduled dose for repeat serum vedolizumab concentration. Once the subject's serum vedolizumab is ≤90 µg/mL, dosing will resume at the next lower dose (see Section 6.1).

The Med ID of the study drug to be dispensed will then be provided by the IRT by email notification to the site pharmacist/nurse. If sponsor-supplied study drug is lost or damaged, the site staff can request a replacement from the IRT.

Refer to IRT manual provided separately. At subsequent drug-dispensing visits, the investigator or designee will again contact the IRT to request additional study drug for a subject.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule and will provide it to the IRT Vendor prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel. Eligible subjects will be randomized to the Standard Dosing Arm or the Dose Optimization Arm of vedolizumab IV in a 1:1 ratio as assigned by IRT. Randomization will be stratified by TNF-antagonist naïve or failure status.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee. The site will maintain source documents in addition to entering data into the IRT.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (vedolizumab IV), the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the Med ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (vedolizumab IV) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date, and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to

the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator's designee administering the study drug infusion must complete an individual subject accountability log to document if infusion was complete or if incomplete and study drug was returned to the pharmacy, including the date and amount returned to the pharmacy, and including the initials, seal, or signature of the person administering the infusion.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2. Informed consent must be obtained before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned per IRT as described in Section 8.2 to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

Informed consent must be obtained prior to the collection, storage, and analysis of the PGx samples. Subjects will have the capability to opt in to the PGx informed consent.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity (as applicable), race as described by the subject, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent.

Ongoing conditions are considered concurrent medical conditions (see Section 9.1.10).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent. Medication history should be captured on the Medication History/Concomitant Medications eCRF page.

In addition, all prior biologic and any medication history for the treatment of UC disease with the reason for discontinuation, that stopped at or prior to signing of informed consent, is to be collected at Screening for subjects where possible. Any prior UC disease treatment should be captured on the Prior UC Disease Treatment eCRF only, and UC treatments started after signing the informed consent, should be captured on the Concomitant Medications eCRF page only.

9.1.3 UC Disease History

UC history collected at Screening will include details of UC diagnosis, disease severity, surgery, hospitalizations, and extraintestinal manifestations. After signing of informed consent all subjects should have UC disease included on the Concurrent Medical Conditions eCRF page.

9.1.4 Physical Examination Procedure

A physical examination will be performed at Screening and Baseline/Day 1 and will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations at all other visits should assess clinically significant changes from the Baseline/Day 1 assessment.

9.1.5 Weight, Height

A subject's height will be measured at the Screening visit; weight will be measured at Screening, Day 1, and Week 30 visits. Both measurements will be collected while the subject is wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (bpm) and will be collected at every visit.

On dosing days, vital signs are taken predose.

9.1.7 Primary Efficacy Measurement

Primary and secondary efficacy assessments during the Randomized Treatment Period will be based on both complete and partial Mayo scores derived from subject diary entries, physician's global assessment, and flexible sigmoidoscopy. A complete Mayo score will be obtained at Screening to determine eligibility along with confirmation of disease location. The subject must have evidence of UC proximal to the rectum (≥15 cm of involved colon) prior to start of vedolizumab IV dosing.

Results obtained during Screening will be the Baseline complete Mayo score. Sigmoidoscopy will be done during Screening and Week 30/Early Termination (ET) Visit, and complete Mayo score will be calculated for these visits. The investigator or designee will record the complete Mayo score in the subject's source documents, with the endoscopic component subscore being provided by the central reader at Screening only. For Week 30, the investigator or designee will use the local endoscopic component subscore to calculate the complete Mayo score. Seven days of completed diary data prior to each study visit is required for Mayo calculation (not including the day before the preparation day, the day of, and the day after the flexible sigmoidoscopy is performed).

A partial Mayo score will be derived for the visits at which endoscopy will not be performed and as listed in Schedule of Study Procedures (Appendix A). These scores will be used to determine clinical response during the study.

The Mayo endoscopic subscore determination of mucosal healing (as defined in Section 3.5) will be based upon central readings to eliminate assessment bias.

Refer to Appendix E for information on the Mayo Scoring System for UC.

9.1.7.1 Diary Completion and Review

Diary entries will be made daily by subjects and will be used for Mayo score calculation. During Screening, subjects will be instructed on how to appropriately complete the daily diary. The symptoms of UC must be recorded throughout the study, including the screening period. Entries should be reviewed and monitored by the study staff.

Because the flexible sigmoidoscopy preparation and the procedure itself can interfere with the assessment of other clinical parameters, diary entries used to calculate the complete Mayo score should not be taken from the day before (the preparation day), the day of, and the day after the flexible sigmoidoscopy is performed.

9.1.7.2 Flexible Sigmoidoscopy and Biopsy

Flexible sigmoidoscopy will be performed at Screening (within 28 days of first dose) and Week 30 (or ET Visit), and the results will be used for calculation of the complete Mayo score for these visits. For subjects without cancer surveillance endoscopy performed in the last 12 months, the investigator can perform a colonoscopy at Screening. All endoscopies (Screening and Week 30) will be centrally read. For Week 30, the investigator or designee will use the local endoscopic component subscore to calculate the complete Mayo score. On the days sigmoidoscopy is done, biopsy samples will be collected from all subjects to possibly evaluate changes in histology.

During screening endoscopic evaluation, 2 biopsies should be taken from the rectum, 2 from the sigmoid, and 2 from the descending colon (if evaluated) taken from the most severely affected areas. If the descending is evaluated and found to be normal, 2 biopsies should also be taken regardless in order to provide a means of comparison at the final visit (Week 30/ET) assessment from that segment. At the Week 30/ET endoscopic assessment, 2 biopsies should again be taken from each of the 3 segments, again from the area most severely affected if inflamed and also if normal (which demonstrates healing) to provide a means of comparison from Baseline. Please see Laboratory Manual for additional collection information.

All biopsy samples collected per protocol will be centrally stored and analyzed at the end of the study. Although it is permissible for the investigator to take additional biopsy samples as deemed necessary for standard of care management of the patient during the protocol required colonoscopy/sigmoidoscopy, these will be considered as occurring outside the protocol. Such collection, handling and analyses of the additional samples will be and remain the responsibility of the investigator.

9.1.8 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication used (from signing of informed consent through the

last scheduled follow-up visit, 18 weeks after last dose of study drug), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.9 Documentation of Concomitant Procedures

At each visit, subjects will be asked whether they have had any UC-related events since their last visit including hospitalizations, bowel surgeries, or UC-related procedures that are not part of the protocol. The timing of the event will be collected relative to the start of treatment on Day 1 of the study through the last clinic visit (Follow-up Visit, 18 weeks after the last dose of study drug). All events with timing will be recorded in the eCRFs. The underlying symptom or diagnosis should correspondingly be recorded as an AE as applicable.

9.1.10 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at the Screening examination. The condition (ie, diagnosis) should be described.

9.1.11 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures at the time points specified in the Schedule of Study Procedures in Appendix A. The maximum volume of blood at any single visit is approximately 66 mL, and the approximate total volume of blood for the study is up to 252 mL for subjects with Q4W dosing (this will be less for subjects with Q8W dosing or the Standard Arm). Details of these procedures and required safety monitoring will be given in the laboratory manual.

Clinical laboratory tests to be performed in this study are summarized in Table 9.a. Refer to the Schedule of Study Procedures in Appendix A for timing of all assessments. See the Laboratory Manual for testing regimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	ALT	Bilirubin
WBC w/differential	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	Amylase	Ketones
Platelets	Lipase	Leukocyte esterase
PT/INR (a)	AST	Nitrite
	Total and direct bilirubin (b)	pH
	Total protein	Protein
	Creatinine	Specific Gravity
	Blood urea nitrogen	Microscopic (to be obtained in the event of positive leukocyte esterase or blood, will include WBCs, RBCs, and cast[s])
	Creatine kinase	
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Bicarbonate	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	

Other:
Collect per Appendix A

Serum/Plasma	Urine	Stool
CRP	Urine pregnancy hCG	Fecal calprotectin
HIV test	(female subjects of childbearing potential)	*C.difficile* toxin
Hepatitis panel, including HBsAg and anti-HCV		
AVA		
PGx sample (optional)		
FSH (c)		
QuantiFERON for TB		
Beta hCG (female subjects of childbearing potential)		

FSH=follicle-stimulating hormone, GGT= γ-glutamyl transferase, hCG=human chronic gonadotropin, PT=prothrombin time, RBC=red blood cell.
(a) PT/INR to be collected at Baseline and then only if liver function tests (LFTs) are elevated at subsequent visits.
(b) Direct bilirubin is measured only if total bilirubin is elevated.
(c) FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented) and not surgically sterile. The FSH result must be >40 IU/mL for the subject to be permitted not to use adequate contraception.

Central laboratories will perform laboratory tests for hematology, serum chemistries, and urinalysis as well as specialty testing outlined above with the exception of the urine pregnancy tests, which will be done on site.

All Screening laboratory tests can be repeated once at the discretion of the principal investigator.

The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Refer to the Schedule of Study Procedures in Appendix A.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

(Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

9.1.12 Fecal Calprotectin Sample Collection

A stool sample will be collected for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity, as shown in the Schedule of Study Procedures in Appendix A.

9.1.13 Stool Sample for *C. difficile*

A stool sample will be obtained to perform *C. difficile* assay. A sample will be collected and cultured during Screening and at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.

9.1.14 Contraception and Pregnancy Avoidance Procedure

9.1.14.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 18 Weeks after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.14.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 18 Weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below). In addition they must be advised not to donate ova during this period.

9.1.14.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

*A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

**Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

    - Non-Hormonal Methods:

      Intrauterine device (IUD).

      Bilateral tubal occlusion.

      Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).

      True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 18 weeks after last dose.

    - Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method.

        – Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;

          Oral.

Intravaginal (eg, ring).

Transdermal.

– Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;

Oral.

Injectable.

Implantable.

2. Unacceptable methods of contraception are:
   – Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   – Spermicides only.
   – Withdrawal.
   – No method at all.
   – Use of female and male condoms together.
   – Cap/diaphragm/sponge without spermicide and without condom.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study.
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)?
      iv. Is there a chance you could be pregnant?

5. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine hCG pregnancy test as close as possible and prior to receiving any dose of Lead-in medication (ie, standard of care) and study medication and at the Week 30/Final Visit and Safety Follow-up Visit.

9.1.14.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the recommendations previously described in Section 9.1.14.3 item 4.

9.1.15 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. The subject will be withdrawn as per the procedures in Section 7.6. In addition, any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of study medication, eg, after Day 1, or within 18 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received.

All pregnancies in subjects on study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.16 ECG Procedure

A standard 12-lead ECG will be recorded at Screening. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

9.1.17 PGx Sample Collection

When sampling of whole blood for pharmacogenomic analysis occurs, every subject must sign informed consent/be consented in order to participate in the PGx part of the study.

Deoxyribonucleic acid (DNA) forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "Pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to vedolizumab.
- Finding out more information about how vedolizumab works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to vedolizumab.
- Identifying variations in genes related to the biological target of vedolizumab.

This information may be used, for example, to develop a better understanding of the safety and efficacy of vedolizumab and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design and study methods of future research studies.

Two whole blood samples (3 mL per sample) for DNA isolation will be collected before dosing on Day 1 from each subject, into plastic potassium ethylenediamine-tetraacetic acid (K_2EDTA) spray-coated tubes, and stored under frozen conditions. A portion of the DNA sample will be used to explore FcRn polymorphisms and its association with drug clearance.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. In addition, if the DNA sample was not collected at the designated time point described in the protocol, it can be collected at a later time point.

Two whole blood samples (2.5 mL per sample) will be collected before dosing on Day 1 for ribonucleic acid (RNA) pharmacogenomic analysis from each subject in the study, into a PaxGene tube, and stored under frozen conditions.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with an 8-digit subject ID (the 5-digit site number plus the 3-digit subject identification number).

The samples will be stored for no longer than 15 years after completion of the vedolizumab study and/or until the drug development of vedolizumab is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. "Stored samples" are defined as samples that are coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of study drug or related drugs.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.1.18 Immunogenicity Sample Collection

Blood specimens for the assessment of AVA will be collected as shown in the Schedule of Study Procedures in Appendix A. A sample will be assessed for neutralizing AVA if AVA is detected.

Serum titers of AVA will be determined using a validated assay. Neutralizing AVA will be determined using a validated assay.

9.1.19 PK Sample Collection

Blood samples (one 5-mL sample per scheduled time) to measure serum vedolizumab concentration will be collected into red-top Vacutainers according to the Schedule of Study Procedures in Appendix A. The actual date and time of sample collection will be recorded on the source document and eCRF.

PK samples must be collected on the same day as the visit date and prior to dosing (on the days of vedolizumab dosing).

Serum concentrations of vedolizumab will be measured using a validated assay.

9.1.20 Pharmacodynamic and Exploratory Biomarker Assessments

Additional blood samples will be collected at Baseline (Appendix A) for measurement of cellular biomarkers that may correlate with response to vedolizumab.

9.1.21 Tuberculosis Screening

All subjects will complete TB screening to determine eligibility. All subjects must complete either a QuantiFERON test or a tuberculin skin test within 30 days of Screening or at Screening. Chest X-ray should be completed if high risk for TB or indeterminate skin test or QuantiFERON. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 7.2.

9.1.22 PML Checklist

Clinic staff will administer the subjective PML checklist during Screening to exclude subjects with positive responses from enrolling into the study. The subjective PML checklist will be administered (prior to IV dosing, if applicable) at each visit, as shown in Appendix A, to evaluate symptoms suggestive of PML. Any subjects reporting signs or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation, as described in the Risk Assessment and Management Program for PML (RAMP) in Section 11.1.1. The symptoms from a positive PML checklist will be recorded as an AE.

9.1.23 Patient Reported Outcome Measures

Subjects will complete the IBDQ at the time points shown in the Schedule of Study Procedures in Appendix A.

The IBDQ is a valid and reliable [35] instrument used to assess quality of life in adult patients with IBD. It includes 32 questions on 4 domains of HRQOL: Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Patients are asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224. An increase of ≥16 points in the IBDQ total score represents a clinically meaningful improvement in health-related quality of life of patients [36]**.** A total IBDQ score ≥170 is associated with clinical remission [36,37].

9.1.24 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible during screening, the investigator should contact the IRT as a notification of screen failure and complete the Screen Failure eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused.

Subjects who fail screening may be rescreened once. Subjects undergoing rescreening must be reconsented and assigned a new subject number by IRT.

9.1.25 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria at Baseline/Day 1 are eligible for enrollment into the Lead-in Period of the study.

At Week 6 subjects will be assessed for eligibility for randomization into the Randomized Treatment Period of the study based on the criteria described in Section 6.1. If the subject is found to be not eligible for randomization, the investigator should record the primary reason for Lead-in failure (Section 9.1.26) on the applicable eCRF.

9.1.26 Documentation of Lead-in Failure

Investigators must account for all subjects enrolled into the Lead-in Period.

If the subject is found to be not eligible for randomization during the Lead-in Period or will not be continuing into the Randomization Period for other reasons, the investigator should contact the IRT as a notification of Lead-in Period failure and complete the appropriate eCRF.

The primary reason for Lead-in Period failure is recorded in the eCRF using the following categories:

- Subject was determined to be a responder.
- Subject was a nonresponder with serum vedolizumab concentrations above a predefined vedolizumab concentration threshold (≥50 µg/mL)).
- PTE/AE.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail the Lead-in Period should not be reused.

9.2 Monitoring Subject Treatment Compliance

A vedolizumab IV dispensing log, including records of drug received from the sponsor and volume of vedolizumab IV dispensed to each subject intravenously, will be maintained by the site.

If a subject is persistently noncompliant with the study medication (ie, fails to keep scheduled study visits), it may be appropriate to withdraw the subject from the study.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Schedule of Study Procedures in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Period

Subjects will be screened within 28 days prior to Enrollment. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects can be enrolled at any time during the Screening period provided that all screening procedures have been completed and eligibility has been confirmed. See Section 9.1.24 for procedures for documenting screening failures. Procedures to be completed at Screening Visit can be found in the Schedule of Study Procedures in Appendix A.

9.3.2 Enrollment and Lead-in Period

Enrollment into the Lead-in Period will take place on Day 1. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for enrollment, the subjects will be enrolled using the IRT as described in Section 8.2. All subjects with moderately to severely active UC who are eligible for treatment with vedolizumab IV will receive vedolizumab IV 300 mg for the Lead-in Period at Day 1 and Week 2 as described in Section 6.1.

Subjects will return to the clinic at Weeks 5 and 6 for assessments that will determine if they are eligible for randomization into the Randomized Treatment Period or are lead-in failures. The procedures performed and documented during Day 1 and Weeks 2, 5, and 6 of the Lead-in Period are shown in the Schedule of Study Procedures in Appendix A.

9.3.3 Randomization (Week 6) and Randomized Treatment Period

If the subject has met the serum vedolizumab concentration threshold defined as having high vedolizumab clearance, based on a predefined Week 5 serum vedolizumab concentration threshold (<50 µg/mL), and has met the nonresponder criteria at Week 6, the subject will be randomized at Week 6 using the IRT as described in Section 8.2. Subjects will be administered the assigned regimen of study drug as described in Section 6.1. Procedures and subsequent dosing and dose adjustments will be performed and documented according to the Schedule of Study Procedures in Appendix A.

Subjects who are determined to be responders or are nonresponders at Week 6 with levels above a predefined serum vedolizumab concentration threshold (≥50 µg/mL) at Week 5 (ie, Lead-In Failures) will not be randomized and will receive the Week 6 study drug dose (300 mg) and thereafter appropriate treatment per physician discretion. These subjects will be followed for up to 18 weeks and receive a LTFU safety survey by telephone call 6 months after the last dose (Week 6) of study drug according to the Schedule of Study Procedures in Appendix A.

9.3.3.1 Lead-in Failures

Subjects who are Lead-in Failures will perform all procedures for Week 6 as per the Schedule of procedures (Appendix A). No redistribution of patient diaries will be made for these subjects.

9.3.4 Randomized Treatment Period and Dose Regimen Selection

Sites will enter the subject's Week 5 vedolizumab serum concentration into the IRT in order to receive their assigned dosing regimen.

At Week 14 and beyond, for subjects randomized into the Dose Optimization Arm, the subject's most recent preceding serum vedolizumab concentration (eg, Week 13 PK sampling prior to Week 14 dosing) will be entered into the IRT in order to confirm and continue their assigned dosing regimen.

Subjects will follow the relevant dosing and visit schedule as per the Schedule of Study Procedures in Appendix A.

9.3.5 Final Visit or Early Termination

For randomized subjects, final treatment period visit procedures will be performed at Week 30 or at the ET Visit, if applicable, according to the Schedule of Study Procedures in Appendix A.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.6 Week 40 (Q8W)/Week 44 (Q4W) Follow-up (18 Weeks Post-Treatment)

For all enrolled subjects, follow-up will begin the first day after the last dose of vedolizumab IV and will continue for 18 weeks. This follow-up visit will be scheduled to assess safety for all subjects and for AVA assessments for all subjects who stopped vedolizumab IV during study as per the Schedule of Study Procedures in Appendix A.

9.3.7 Long-Term Follow-Up Safety Survey (6-Months Post-Treatment)

Upon completion of or ET from the study, all subjects will complete a LTFU safety survey by telephone. This questionnaire will be administered at 6 months from the last dose of study drug.

9.3.8 Unscheduled Visits (if applicable)

Subjects may return to the study center for unscheduled visits as needed. Unscheduled visits can be performed when the subject has a study-related issue in between regular visits (ie, SAE follow-up, additional PK samples, LFT elevations).

At any unscheduled visits, the following procedures will be performed and documented as applicable:

- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Any additional procedures included in the protocol may be conducted at the judgment of the investigator.

Standard-of-care visits (routine check-ups) should not be captured as an unscheduled visit in eCRF. However, if the visit is due to disease exacerbation the procedures described in Section 9.3.9 should be performed.

9.3.9 Unscheduled Visits Due to Disease Exacerbation

Subjects who are seen by the investigator or site staff at a time point not required by the protocol (ie, unscheduled visit) due to disease exacerbation will undergo the following:

- Physical examination.
- Vital signs assessment.
- Diary review.

- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Clinical chemistry and hematology, as indicated.
- Partial or complete Mayo score.
- Flexible sigmoidoscopy, if indicated.
- PK sample collection.
- AVA sample collection.
- *C. difficile*, if indicated.

There is no minimum time for repeat evaluation by unscheduled visit in order to determine if a subject has disease exacerbation. In general, however, enough time should be provided for clinically meaningful change to occur.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected according to the Schedule of Study Procedures in Appendix A. The genetic material will be preserved and retained for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The blood samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided pharmacogenomic samples can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Special Interest AEs

An AESI, either serious or nonserious, is an AE of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

AESIs for this compound are serious infections (and include opportunistic infection such as PML), liver injury, malignancies, infusion-related or systemic reactions, and hypersensitivity, as described in further detail as follows:

10.1.5.1 Hypersensitivity Reactions (Including Infusion-Related Reactions)

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab IV; hence such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator, however, subjects may be administered premedication prior to any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of administration.

Vedolizumab IV should be administered by a health care practitioner prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical

support measure should be available for immediate use. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

Subjects and caregivers will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injection site pain, redness and/or swelling, etc. that may represent an administration-related reaction (ie, infusion-related reaction) to study medication. Subjects will be asked to report administration-related AEs to the sites immediately as they are experienced. Appropriate treatment and follow-up will be determined by the investigator. If signs or symptoms of an administration-related reaction are observed during the administration of study medication, it should be immediately discontinued and the subject treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication and investigator supervision) at the discretion of the investigator. Subjects with a severe or serious administration-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs, severe injection site reactions) must be withdrawn from the study.

In all cases of administration-related reaction, the medical monitor must be informed as soon as practical. The disposition of subjects with less severe administration-related reactions should be discussed with the medical monitor.

10.1.5.2 Serious Infections

Subjects will be monitored for signs and symptoms of infection and for lymphopenia during the study. Subjects with signs and symptoms suggestive of infections, including GI infections, will be treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Withholding or terminating study drug administration may be considered as described in Section 7.5.

10.1.5.3 Malignancy

All cases of malignancies that are detected during the study will be reported as AEs. Local medical practices for the management of malignances will apply. Subjects with history of malignancy (except for specific cancers) or at high risk for malignancy will be excluded from the study per the exclusion criteria.

10.1.5.4 Other

Other special interest AEs include liver injury and PML, which are discussed in Sections 10.2.3 and 11.1.1, respectively.

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.

- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Start of PTE collection:

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen failure before Day 1. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Start of AE collection:

AEs must be collected from the time that the subject is first administered study medication (Day 1).

End of AE collection:

Routine collection of AEs will continue for 18 weeks following the last dose of study medication.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date (and time).
3. Severity.
4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

The IBDQ and patient diary will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 Special Interest AE Reporting

If an AESI that occurs during the treatment period or the follow-up period is considered to be clinically significant based on the criteria in Section 10.1.5, it should be recorded in a special

interest AE eCRF or SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

The special interest AEs have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed in the eCRF and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s)
- Causality assessment.

A paper SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1 in the event that the eCRF is not available.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.11 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No data safety monitoring committee will be used in this study.

11.1 PML Independent Adjudication Committee

A PML Independent Adjudication Committee (IAC) will be instituted for this study. The PML IAC will consist of a panel of leading PML experts, including a neurologist, neuroradiologist, and a virologist.

11.1.1 Risk Assessment and Management Program (RAMP) for PML

Natalizumab (TYSABRI), another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the central nervous system. PML is caused by the John Cunningham virus (JCV) and typically only occurs in patients who are immunocompromised [38,39]. Natalizumab is a pan-α4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to vascular cell adhesion molecule-1 (VCAM-1) and MAdCAM-1 [40,41]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [24] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical trials with vedolizumab to date, a risk of PML cannot be ruled out.

To address the theoretical risk of the development of PML in subjects treated with vedolizumab IV, the sponsor, with input from renowned PML experts, has developed a RAMP program. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the RAMP Study Manual.

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Subjects are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML subjective symptom checklist. Subjects with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab IV clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm). The next dose of study drug will be held until the evaluation is complete and results are available. Subsequent doses of study drug will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. An IAC has been established as part of the RAMP program to review new neurological signs and symptoms potentially consistent with PML, and will provide input regarding subject evaluation and management as defined in the IAC charter.

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML, and subjects will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and subjects about PML and the RAMP procedures will be distributed to all sites and are included in the study manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Subjects will receive training and educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary(WHODRUG).

12.1 Electronic CRFs

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor or delegated contract research organization (CRO) will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site

and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The full analysis set (FAS) will include all randomized subjects who receive at least 1 postrandomization dose of study drug (ie, in the Randomized Treatment Period). Subjects in this set will be analyzed according to treatment they were randomized to receive (intent-to-treat [ITT]).

The safety analysis set will include all enrolled subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment received.

The PK set will include all randomized subjects who receive at least 1 postrandomization dose of study drug (ie, in the Randomized Treatment Period) and have at least 1 measurable postrandomization concentration of vedolizumab.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all enrolled subjects by treatment group (nonrandomized vedolizumab IV and randomized treatment groups) and overall. Additional summaries will be provided for the FAS and other analysis sets, as appropriate. For continuous variables, summary statistics (nonmissing values, mean, median, SD, minimum and maximum) will be generated. For categorical variables, the counts and percentages of each possible value will be generated.

Medical history and concurrent medical conditions will be summarized by system organ class and preferred term. Medication history and concomitant medications will be summarized by preferred name.

13.1.3 Efficacy Analysis

All efficacy analyses will be based on the FAS, with the exception of corticosteroid-free remission which will be based on the subset of the FAS who are taking concomitant oral corticosteroids at Baseline.

All proportion-based primary, secondary and additional efficacy endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion by treatment group. The difference in proportions between treatment groups along with the 95% confidence interval will be presented. The primary efficacy analyses will be based on logistic model with treatment as

a factor, natural logarithm of trough concentration at Week 6 and other important covariates as explanatory variables. Odds ratio and its 95% confidence interval for treatment effect will be provided. All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis.

The additional efficacy endpoints of change from Baseline in CRP and fecal calprotectin will be summarized descriptively by time point and treatment group. A mixed model repeated measures analysis with treatment, visit, treatment by visit as fixed effect and its baseline value as a covariate will be performed. An unstructured covariance matrix is assumed. The LS mean, p-value and 2-sided 95% confidence interval of treatment difference will be provided.

13.1.4 PK Analysis

PK analyses will be performed on the PK set. Measured serum vedolizumab concentrations will be summarized by time using descriptive statistics. Individual serum concentration versus time data will be presented in a data listing.

C_{trough} will be derived and further details will be provided in the SAP. C_{trough} will be summarized using descriptive statistics (nonmissing values, mean, SD, %CV, median, minimum, and maximum).

The additional endpoint, the proportion of subjects with C_{trough} below the threshold target of 18.4 µg/mL at Week 14 and 12.7 µg/mL at Week 30, will be presented by treatment group.

Further analysis will be performed as deemed necessary and will not be reported in the clinical study report (CSR). These analyses will be part of a separate report.

13.1.5 Other Analyses

The following additional endpoints will be analyzed on the FAS.

Change from Baseline in IBDQ total score and IBDQ domain scores will be summarized descriptively by time point and treatment group.

The proportion of subjects with positive AVA (transient and persistent) and the proportion of subjects with positive neutralizing AVA during the study will be summarized by treatment group. The impact of AVA on PK, efficacy, and safety will be examined.

A positive AVA subject is defined as a subject who has at least 1 positive AVA result in any postbaseline sample, and is further categorized as:

- Transiently positive: defined as subjects with confirmed positive AVA in 1 sample at a postdose visit.
- Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples at postdose visits.

13.1.6 Safety Analysis

All safety analyses will be performed using the safety analysis set and will be split into prerandomization and postrandomization periods. The nonrandomized vedolizumab IV group as well as the randomized treatment groups will be summarized. No statistical inference will be made for safety analyses.

The number and percentage of subjects with treatment-emergent adverse events ([TEAEs], defined as any AEs, regardless of relationship to study drug), AESIs (ie, serious infections, PML, malignancies, liver injury, infusion reactions), and SAEs which occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug will be summarized by MedDRA system organ class, high level term, and preferred term overall, by severity, and by relationship to vedolizumab for each treatment group. Separate summaries will also be generated for treatment-related adverse events overall and by severity.

Change from Baseline in clinical laboratory tests and vital signs will be summarized by time point and treatment group. Subjects with markedly abnormal values for laboratory tests and vital signs will be tabulated.

Physical examination findings and PML checklist data will be presented in data listings.

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis will be conducted for the purpose of publication when all subjects have completed the Week 30 Final Visit or ET Visit. No study decisions will be made based on the interim results and subjects will continue to the Follow-up Period.

All available data will be included in the interim analysis. Data which can be considered final at Week 30 (all data except AEs, concomitant medications, and UC-related procedures and any Follow-up Visit data) will be cleaned and locked prior to the analysis.

As all efficacy endpoints are measured at Weeks 14 or 30 there is no alpha adjustment required in the statistical analyses. Further details on the interim analysis will be documented in the SAP.

13.3 Determination of Sample Size

The sample size was based on an estimate of precision and not on statistical power considerations. A total sample size of approximately 250 subjects enrolled to achieve approximately 100 subjects randomized at Week 6, including 50 subjects per treatment group, will be sufficient to provide 95% confidence intervals for mucosal healing rates with a half width no wider than +/-13.9%. In addition, the maximum width of the 95% confidence intervals (2-sided) for the difference in mucosal healing rates between the 2 groups will be no wider than +/-19.6%. If there is a high rate of patient drop out from the study, additional patients may be added.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. The deviation should be documented on the Significant Protocol Deviation eCRF by the site and reviewed/acknowledged by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration (FDA),the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

	Screening	Lead-in (week)			Randomized Treatment Period (week)								Follow-up (c)	LTFU Phone Call (d)
Week		**Day 1/ BL (a)**	**2**	**5**	**6 (b) Decision**	**10**	**13**	**14**	**18**	**22 (EOT Q8wk)**	**26 (EOT Q4wk)**	**30 Final Visit/ET**	**18 wks from EOT**	**6-months from EOT**
Study Day	**-28 to -1**	**1**	**15±3**	**36±3**	**43±3**	**71±3**	**92±3**	**99±3**	**127±5**	**155±5**	**183±5**	**211±5**	**Q8 281±7 Q4 309±7**	**Q8 337±7 Q4 365±7**
Visit Window (Days):		1	**Days 12-18**	Days 33-39	Days 40-46	Days 68-74	Days 89-95	Days 96-102	Days 122-132	Days 150-160	Days 178-188	Days 206-216	Q8 Days 274-288 Q4 Days 302-316	Q8 Days 330-344 Q4 Days 358-372
Visits that apply to Lead-in Failures	X	X	X	X	X								X	X
Visits that apply to Standard Arm	X	X	X	X	X			X		X		X	X	X
Visits that apply to Dose Optimization Arm	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X													
Access IRT	X	X	X		X	X		X (e)	X (e)	X (e)	X (e)	X		
Lead in Period inclusion/exclusion criteria	X	X												
Randomized Treatment Period inclusion criteria					X									
Demographics/medical history/concurrent medical conditions	X													
UC disease history	X													
Medication history/Prior UC disease treatments	X													

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening	Lead-in (week)			Randomized Treatment Period (week)								Follow-up (c)	LTFU Phone Call (d)
Week		**Day 1/ BL (a)**	**2**	**5**	**6 (b) Decision**	**10**	**13**	**14**	**18**	**22 (EOT Q8wk)**	**26 (EOT Q4wk)**	**30 Final Visit/ET**	**18 wks from EOT**	**6-months from EOT**
Study Day	**-28 to -1**	**1**	**15±3**	**36±3**	**43±3**	**71±3**	**92±3**	**99±3**	**127±5**	**155±5**	**183±5**	**211±5**	**Q8 281±7 Q4 309±7**	**Q8 337±7 Q4 365±7**
Visit Window (Days):		1	**Days 12-18**	Days 33-39	Days 40-46	Days 68-74	Days 89-95	Days 96-102	Days 122-132	Days 150-160	Days 178-188	Days 206-216	Q8 Days 274-288 Q4 Days 302-316	Q8 Days 330-344 Q4 Days 358-372
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collection of concomitant procedures		X	X	X	X	X	X	X	X	X	X	X	X	
Tuberculosis QuantiFERON or skin test (f)	X													
Hepatitis, HIV	X													
Physical examination	X	X						X				X	X	
Vital signs (g)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight and height (g)	X	X										X		
Flexible sigmoidoscopy (h)	X											X		
Complete Mayo Score	X											X (i)		
Partial Mayo Score		X	X		X	X		X	X	X	X	X (i)		

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening	Lead-in (week)			Randomized Treatment Period (week)							Follow-up (c)	LTFU Phone Call (d)
Week		**Day 1/ BL (a)**	**2**	**5**	**6 (b) Decision**	**10**	**13**	**14**	**18**	**22 (EOT Q8wk)**	**26 (EOT Q4wk)**	**30 Final Visit/ET**	**18 wks from EOT**	**6-months from EOT**
Study Day	**-28 to -1**	**1**	**15±3**	**36±3**	**43±3**	**71±3**	**92±3**	**99±3**	**127±5**	**155±5**	**183±5**	**211±5**	**Q8 281±7 Q4 309±7**	**Q8 337±7 Q4 365±7**
Visit Window (Days):		1	**Days 12-18**	Days 33-39	Days 40-46	Days 68-74	Days 89-95	Days 96-102	Days 122-132	Days 150-160	Days 178-188	Days 206-216	Q8 Days 274-288 Q4 Days 302-316	Q8 Days 330-344 Q4 Days 358-372
PK samples for vedolizumab (j)		X	X	X	X	X	X	X	X	X	X	X	X	
Dose Regimen Assignment (k)					X									
Vedolizumab (IV) lead-in period (m)		X	X		X									
Vedolizumab (IV) randomization period (m)					X	X		X	X	X	X			
Clinical laboratory testing	X	X	X		X	X		X	X	X	X	X	X	
PT/INR (n)		X												
Exploratory biomarker sample		X												
Urinalysis	X											X		
CRP	X	X			X			X				X		
PGx samples (o)		X												
AVA testing (p)		X			X			X		X		X	X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening	Lead-in (week)			Randomized Treatment Period (week)								Follow-up (c)	LTFU Phone Call (d)
Week		**Day 1/ BL (a)**	**2**	**5**	**6 (b) Decision**	**10**	**13**	**14**	**18**	**22 (EOT Q8wk)**	**26 (EOT Q4wk)**	**30 Final Visit/ET**	**18 wks from EOT**	**6-months from EOT**
Study Day	**-28 to -1**	**1**	**15±3**	**36±3**	**43±3**	**71±3**	**92±3**	**99±3**	**127±5**	**155±5**	**183±5**	**211±5**	**Q8 281±7 Q4 309±7**	**Q8 337±7 Q4 365±7**
Visit Window (Days):		1	**Days 12-18**	Days 33-39	Days 40-46	Days 68-74	Days 89-95	Days 96-102	Days 122-132	Days 150-160	Days 178-188	Days 206-216	Q8 Days 274-288 Q4 Days 302-316	Q8 Days 330-344 Q4 Days 358-372
Pregnancy test (serum and urine) (hCG) (q)	X	X	X		X	X		X	X	X	X	X	X	
FSH (r)	X													
ECG	X													
PML checklist (s)	X	X	X		X	X		X	X	X	X	X	X	
PML wallet card	X											X (t)		
IBDQ		X						X				X		
Patient diary	X	X	X	X	X (l)	X	X	X	X	X	X	X		
Stool sample for *C. difficile* Test	X													
Stool sample for fecal calprotectin (u)	X				X			X				X		
PTE assessment (v)	X	X												
AEs (w)		X	X	X	X	X	X	X	X	X	X	X	X	
LTFU questionnaire via phone call														X

BL=baseline, EOT=end of treatment.
(a) Assessments to be completed predose.
(b) Confirm Week 5 PK results before the Week 6 visit.

(c) 18 Week posttreatment follow-up is Week 40 (Q8W) and Week 44 (Q4W). If a subject in the Dose Optimization Arm dose is lowered to 300 mg Q8W dosing and the last dose is week 26, they should follow the Q4W schedule and windows for the 2 Follow-up Visits.
(d) LTFU telephone call to be performed 6 months after last dose of study drug for all subjects enrolled in the study and receiving at least 1 dose of study medication. This is expected to occur for Lead-in failures no later than Week 32 and for Randomized subjects at Week 48 for a Q8W regimen or at Week 52 for Q4W regimen. If a subject in the Dose Optimization Arm dose is lowered to 300 mg Q8W dosing and the last dose is week 26, they should follow the Q4W schedule and windows for the 2 Follow-up Visits.
(e) In Dose Optimization Arm, dosing may be withheld or lowered based on prior serum vedolizumab concentration. If subject switches to the 300 mg Q8W dosing due to high serum vedolizumab concentration, the IRT only needs to be called on dose dispensing visits.
(f) Assessed by QuantiFERON test or a TB skin test reaction at Screening, within 30 days of Screening. See section 9.1.21.
(g) Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (bpm). On dosing days, vital signs are taken predose. Height will be collected only at Screening Visit.
(h) Biopsies to be collected at Screening and Week 30. For subjects without cancer surveillance endoscopy performed in last 12 months, the investigator can perform a colonoscopy at Screening. Evaluation of endoscopy results will be performed by the central reader. All biopsy samples collected per protocol will be centrally stored and analyzed at the end of the study. Although it is permissible for the investigator to take additional biopsy samples as deemed necessary for standard of care management of the patient during the protocol required colonoscopy/sigmoidoscopy, these will be considered as occurring outside the protocol. Such collection, handling and analyses of the additional samples will be and remain the responsibility of the investigator.
(i) Partial Mayo score to be performed if flexible sigmoidoscopy is not performed at this visit.
(j) PK samples for serum vedolizumab on dosing days must be collected predose on the same date as the infusion. If the samples are not collected prior to vedolizumab dosing or not collected on the same day as the infusion, it is a significant deviation. PK samples are also collected on non-dosing visits per Appendix A.
(k) For subjects randomized to the Dose Optimization Arm, dosing regimens will be assigned by the IRT based on the Week 5 serum vedolizumab concentrations.
(l) Not applicable for Lead-in Failures. No redistribution of patient diaries to Lead-in failures.
(m) All subjects will receive treatment with vedolizumab IV per label through Week 2. Nonresponders at Week 6 with serum vedolizumab concentration <50 µg/mL based on Week 5 PK collection will be randomized at Week 6 in a 1:1 ratio to 1 of 2 treatment arms as follows: vedolizumab IV Standard Dosing Arm or Dose Optimization Arm. At Week 6, all subjects who respond or are nonresponders and are above a predefined vedolizumab concentration threshold (≥50 µg/mL) at Week 5 will not be eligible to be randomized into the study, and will receive the Week 6 study drug infusion and thereafter continue to receive appropriate treatment per physician's discretion.
(n) PT/INR to be collected at Baseline and then only if LFTs are elevated at subsequent visits.
(o) Blood samples (for DNA and RNA analysis) will be collected on Day 1.
(p) On dosing days, blood samples must be taken predose.
(q) Women of childbearing potential only. Serum pregnancy test at Screening only; urine pregnancy test should be done thereafter, including before every IV infusion.
(r) FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented) and not surgically sterile. The FSH result must be >40 IU/mL for the subject to be permitted not to use adequate contraception.
(s) PML checklist must be administered at all visits in Appendix A and on dosing days, prior to vedolizumab dosing.
(t) Long-term Follow-up Wallet card will be given to subjects at the last clinical visit.
(u) Stool sample for fecal calprotectin should be the first bowel movement on the day of collection.
(v) PTEs will be captured immediately following the signing of the informed consent at the Screening Visit, up until the first dose of study drug.
(w) Collection of AEs will begin following first dose of study drug and will continue through Wk 40 (for Q8W)/Final Safety Visit or Wk 44 (for Q4W)/Final Safety Visit. Collection of all SAEs will begin once the informed consent is signed and will continue through Week 40 (for Q8W)/Final Safety Visit or Week 44 (for Q4W)/Final Safety Visit.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
13. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study and for 18 weeks after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study and for 18 weeks after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Category(a)
Stool frequency (b)
0 = Normal no. of stools for this patient
1 = 1 to 2 stools more than normal
2 = 3 to 4 stools more than normal
3 = 5 or more stools more than normal
Sub score, 0 to 3
Rectal bleeding (c)
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passes
Sub score, 0 to 3
Findings on endoscopy
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Sub score, 0 to 3; 0 = Normal or inactive disease
Physician's global assessment (d)
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease
Sub score, 0 to 3

(a) The Mayo score ranges from 0–12, with higher scores indicating more severe disease. Partial Mayo score excludes endoscopy and ranges from 0–9.
(b) Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
(c) The daily bleeding score represents the most severe bleeding of the day.
(d) The physician's global assessment acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317 (26):1625-9.

Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Investigator agreement revised to remove provision of package insert.

The primary change occurs in Section 1.2 Approval.

Initial wording:	I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:
Amended wording:	I confirm that I have read and that I understand this protocol, the Investigator's Brochure, ~~package insert~~ and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

Rationale for Change: Investigator brochure was provided to investigators.

Change 2: Subject number to enroll was increased from 200 to 250, to randomize approximately 100 subjects.

The primary change occurs in Section 6.1 Study Design.

Initial wording:	Approximately 200 subjects will be enrolled in order to randomize up to 100 nonresponder subjects with high vedolizumab drug clearance.
Amended wording:	Approximately ~~200~~ **250** subjects will be enrolled in order to randomize ~~**up to**~~ **approximately** 100 nonresponder subjects with high vedolizumab drug clearance.

Rationale for Change: Subject number increased due to a higher than expected lead-in failure rate.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.1 Study Design
- Figure 6.a Schematic of Study Design
- Section 13.3 Determination of Sample Size

Change 3: Site number was increased from 70 to 80.	
The primary change occurs in Section 2.0 STUDY SUMMARY.	
Initial wording:	Estimated total: Approximately 70 in the United States and Canada
Amended wording:	Estimated total: Approximately ~~70~~ **80** in the United States and Canada
Rationale for Change: To add additional sites to contribute to enrollment.	

Change 4: Section 5.2.2 Secondary Endpoints, Day 1 was removed from the complete Mayo score definition of Baseline.

The primary change occurs in Section 5.2.2 Secondary Endpoints.

Initial wording:	Proportion of subjects achieving clinical response, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (Day 1) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point, at Week 30.
Amended wording:	Proportion of subjects achieving clinical response, where clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from Baseline ~~(Day 1)~~ with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point, at Week 30.

Rationale for Change: Screening labs are used to calculate the complete Mayo score.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 3.5 Study Definitions

Change 5: Exclusion Criteria #7, clarified subjects with prior exposure to approved or investigational anti-integrin antibodies are excluded.

The primary change occurs in Section 7.2 Exclusion Criteria.

Initial wording:	The subject has previously received natalizumab, efalizumab, etrolizumab, AMG-181, MAdCAM-1 antibodies, or rituximab.
Amended wording:	The subject has ~~previously received~~ **had prior exposure to approved or investigational anti-integrin antibodies (eg,** natalizumab, efalizumab, etrolizumab, AMG-181, **anti-**MAdCAM-1 antibodies, or rituximab**)**.

Rationale for Change: Clarification of existing text.

Section 2.0 STUDY SUMMARY also contains this change.

Change 6: Exclusion Criteria #8, clarified subjects that previously received approved or investigational Vedolizumab (not just Vedolizumab IV) are excluded.	
The primary change occurs in Section 7.2 Exclusion Criteria.	
Initial wording:	The subject has previously received vedolizumab IV.
Amended wording:	The subject has previously received **approved or investigational** vedolizumab ~~IV~~.
Rationale for Change: Clarification of existing text that any type of vedolizumab is excluded.	

Change 7**:** Exclusion Criteria #11, clarified timing of exclusion is during Screening.	
The primary change occurs in Section 7.2 Exclusion Criteria.	
Initial wording:	The subject has any evidence of an active infection (eg, sepsis, cytomegalovirus, or listeriosis).
Amended wording:	The subject has any evidence of an active infection **during Screening** (eg, sepsis, cytomegalovirus, or listeriosis).
Rationale for Change: Clarification of existing text.	

Change 8**:** Exclusion Criteria #18, clarified timing of exclusion is 2 weeks prior to Screening.	
The primary change occurs in Section 7.2 Exclusion Criteria.	
Initial wording:	The subject has used a topical (rectal) treatment with (5-ASA) or corticosteroid enemas/suppositories within 2 weeks of the administration of the first dose of study drug.
Amended wording:	The subject has used a topical (rectal) treatment with (5-ASA) or corticosteroid enemas/suppositories within 2 weeks ~~of the administration of the first dose of study drug~~ **prior to Screening**.
Rationale for Change: Clarification of existing text.	

Change 9: Exclusion Criteria #25, clarified timing of PML checklist administration.	
The primary change occurs in Section 7.2 Exclusion Criteria.	
Initial wording:	The subject has a positive PML subjective symptom checklist prior to the administration of the first dose of study drug.
Amended wording:	The subject has a positive PML subjective symptom checklist **during Screening or** prior to the administration of the first dose of study drug **on Day 1**.
Rationale for Change: Clarification of existing text.	
Section 2.0 STUDY SUMMARY also contains this change.	

Change 10: Section 7.4.1 Excluded Medications was updated.

The primary change occurs in Section 7.4.1 Excluded Medications.

Initial wording:

The following medications are excluded from use during the study from the time of Screening, unless specified otherwise:

1. TNF-α antagonist infliximab, adalimumab, certolizumab pegol, golimumab, or biosimilar agent.
2. Any treatment for UC other than those listed in Section 7.4.2 (either approved or investigational).
   - From randomization and throughout study, any of the following for the treatment of UC:
     - Nonbiologic therapies (eg, cyclosporine, thalidomide).
     - A nonbiologic investigational therapy.
     - An approved nonbiologic therapy in an investigational protocol.
3. All live vaccines within 30 days prior to randomization, throughout the study treatment period, and for at least 6 months after the last dose of study drug.
4. Either approved or investigational biologic agents for the treatment of non-IBD conditions, other than localized injections (eg, intra-ocular injections for wet macular degeneration).

Amended or new wording:

The following medications are excluded from use during the study from the time of Screening **through the Final Visit/ET (Week 30)**, unless specified otherwise:

1. ~~TNF-α antagonist infliximab, adalimumab, certolizumab pegol, golimumab, or biosimilar agent~~. **Any approved or nonapproved biologic or biosimilar agent for the treatment of IBD.**

~~2. Any treatment for UC other than those listed in Section 7.4.2 (either approved or investigational).~~

- ~~From randomization and throughout study, any of the following for the treatment of UC:~~
  - ~~Nonbiologic therapies (eg, cyclosporine, thalidomide).~~
  - ~~A nonbiologic investigational therapy.~~
  - ~~An approved nonbiologic therapy in an investigational protocol~~.

2. Any approved or nonapproved nonbiologic therapy for treatment of UC in an investigational protocol.

3. Any nonbiologic therapies (eg. cyclosporine, thalidomide) for the treatment

of UC other than those listed in section 7.4.2.

4. ~~All~~ **Any** live vaccines ~~within 30 days prior to randomization, throughout the study treatment period, and for at least~~ **through** 6 months after the last dose of study drug.
5. ~~Either~~ **Any** approved or ~~investigational~~ **nonapproved** biologic ~~agents~~ for the treatment of non-IBD conditions, other than localized injections (eg, intra-ocular injections for wet macular degeneration).
6. **Topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories.**
7. **TPN or albumin.**

Rationale for Change: The excluded medications are not allowed because the subjects may not remain on them throughout the study on a stable dose and any variable that can interfere with primary drug efficacy should be removed.

Change 11: Section 7.4.2 Permitted Medications was updated.

The primary change occurs in Section 7.4.2 Permitted Medications.

Initial wording:

- Probiotics (eg, Culturelle, *Saccharomyces boulardii*)
- Oral 5-ASA compounds.
- 5-ASA or corticosteroid enemas/suppositories, stable for at least 2 weeks prior to Screening.
- Oral corticosteroid therapy for UC up to 30 mg/day is permitted during Screening and upon enrollment. Tapering must be made at the investigator's discretion no later than Week 14. See Section 7.4.2.1.
- Antidiarrheals for control of chronic diarrhea.
- Azathioprine, 6-mercaptopurine, or methotrexate, provided that the dose has been stable for 8 weeks immediately prior to Screening.

Amended wording:

- Probiotics (eg, Culturelle, *Saccharomyces boulardii*) **provided that the subject was receiving them at the Screening Visit and they remain stable throughout the study.**
- Oral 5-ASA compounds **provided that the subject was receiving them at the Screening Visit and that they remain stable throughout the study.**
- ~~5-ASA or corticosteroid enemas/suppositories, stable for at least 2 weeks prior to Screening.~~
- Oral corticosteroid therapy for UC **total of** up to 30 mg/day is permitted during Screening and upon enrollment. Tapering must be made at the investigator's discretion no later than Week 14. See Section 7.4.2.1.
- Antidiarrheals for control of chronic diarrhea.
- Azathioprine, 6-mercaptopurine, or methotrexate, provided that the dose has been stable for 8 weeks immediately prior to Screening **and remain stable throughout the duration of the study.**

Rationale for Change: All concomitant medications that are allowed while the subjects are in the study are to be administered in stable doses throughout the study. Clarification of existing text.

Change 12: Section 7.4.2.1 Corticosteroid Taper, co-administration maximum dose and budesonide taper were added.

The primary change occurs in Section 7.4.2.1 Corticosteroid Taper.

Initial wording:

Oral corticosteroid taper should be initiated by Week 10 and no later than Week 14 according to the following schedule:

- For prednisone doses >10 mg/day (or equivalent), the dose will be reduced at a rate of 5 mg/week until a 10 mg/day dose is reached.
- For prednisone doses ≤10 mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) is reached, the dose will be reduced at a rate of 2.5 mg/week until discontinuation. For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids could be increased up to, but not exceed, the original dose the subject was on at the start of the induction phase. In such cases, the tapering regimen above will be reinitiated within 2 weeks.

Amended wording:

The maximum dose of oral prednisone for the treatment of UC that may be coadministered with vedolizumab IV is 30 mg/day or 9 mg/day budesonide (or equivalent). Oral corticosteroid taper should be initiated by Week 10 and no later than Week 14 according to the following schedule:

- For prednisone doses >10 mg/day (or equivalent), the dose will be reduced at a rate of 5 mg/week until a 10 mg/day dose is reached.
- For prednisone doses ≤10 mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) is reached, the dose will be reduced at a rate of 2.5 mg/week until discontinuation. For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids could be increased up to, but not exceed, the original dose the subject was on at the start of the induction phase. In such cases, the tapering regimen above will be reinitiated within 2 weeks.
- **Budesonide should be reduced 3 mg every 2 weeks until discontinuation.**

Rationale for Change: Up to 30 mg/day of oral corticosteroids is considered the standard of care; any doses higher than that, indicates a more severe disease progression and unlikely to taper the patient.

Change 13: Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject, replacement language was removed.

The primary change occurs in Section 7.6 Procedures for Discontinuation or Withdrawal of a Subject.

Initial wording:	The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit, Final Safety Visit, and the LTFU survey. Discontinued or withdrawn subjects will not be replaced.
Amended wording:	The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit, Final Safety Visit, and the LTFU survey. ~~Discontinued or withdrawn subjects will not be replaced.~~

Rationale for Change: Per Section 13.1.3, if there is a high rate of patient drop out from the study, additional patients may be added.

Change 14: Section 8.1.2 Storage, clarified storage requirements for Vedolizumab IV.	
The primary change occurs in Section 8.1.2 Storage.	
Initial wording:	Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF to 46ºF). A daily temperature log of the drug storage area must be maintained every working day.
Amended wording:	Vedolizumab IV must be stored **in a refrigerator** at 2ºC to 8ºC (36ºF to 46ºF). A daily temperature log of the drug storage area must be maintained every working day.
Rationale for Change: Clarification of existing text.	

Change 15: Section 8.2 Investigational Drug Assignment and Dispensing Procedures, clarified lower dose will resume once serum Vedolizumab is ≤90 µg/mL.

The primary change occurs in Section 8.2 Investigational Drug Assignment and Dispensing Procedures.

Initial wording:	At Week 14 and beyond, for subjects in the Dose Optimization Arm, the investigator or the investigator's designee will enter the subject's most recent preceding serum vedolizumab concentration into IRT prior to dosing. If serum vedolizumab is >90 µg/mL, the next dose will be withheld and subject will be brought back the week before the next scheduled dose for repeat serum vedolizumab concentration. Once the subject's serum vedolizumab is <90 µg/mL, dosing will resume at the next lower dose (see Section 6.1).
Amended wording:	At Week 14 and beyond, for subjects in the Dose Optimization Arm, the investigator or the investigator's designee will enter the subject's most recent preceding serum vedolizumab concentration into IRT prior to dosing. If serum vedolizumab is >90 µg/mL, the next dose will be withheld and subject will be brought back the week before the next scheduled dose for repeat serum vedolizumab concentration. Once the subject's serum vedolizumab is ≤90 µg/mL, dosing will resume at the next lower dose (see Section 6.1).

Rationale for Change: Clarification of existing text.

Change 16: Section 9.1.2 Medication History and Prior UC Disease Treatment eCRF data entry was clarified.

The primary change occurs in Section 9.1.2 Demographics, Medical History, and Medication History Procedure.

Initial wording:	Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent. In addition, all prior biologic and any medication history for the treatment of UC disease with the reason for discontinuation is to be collected for subjects where possible.
Amended wording:	Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent. **Medication history should be captured on the Medication History/Concomitant Medications eCRF page.** In addition, all prior biologic and any medication history for the treatment of UC disease with the reason for discontinuation, **that stopped at or prior to signing of informed consent,** is to be collected **at Screening** for subjects where possible. **Any prior UC disease treatment should be captured on the Prior UC Disease Treatment eCRF only, and UC treatments started after signing the informed consent, should be captured on the Concomitant Medications eCRF page only**.

Rationale for Change: Clarification of existing text.

Change 17: Section 9.1.3 UC Disease History, clarified eCRF data entry for UC disease as concurrent condition.

The primary change occurs in Section 9.1.3 UC Disease History.

Initial wording:	UC history collected at Screening will include details of UC diagnosis, disease severity, surgery, hospitalizations, and extraintestinal manifestations.
Amended wording:	UC history collected at Screening will include details of UC diagnosis, disease severity, surgery, hospitalizations, and extraintestinal manifestations. **After signing of informed consent all subjects should have UC disease included on the Concurrent Medical Conditions eCRF page.**

Rationale for Change: Clarification of existing text.

Change 18: Section 9.1.6 Vital Sign Procedure, 5 minute period for vital sign collection and order of procedure language were removed.

The primary change occurs in Section 9.1.6 Vital Sign Procedure.

Initial wording:	When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and it is recommended that vital signs be obtained within 0.5 hour before or after the scheduled blood draw.
Amended wording:	~~When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and it is recommended that vital signs be obtained within 0.5 hour before or after the scheduled blood draw.~~

Rationale for Change: To allow for more flexibility in time of vital sign collection.

Change 19: Section 9.1.9 Documentation of Concomitant Procedures, clarified last clinic visit.

The primary change occurs in Section 9.1.9 Documentation of Concomitant Procedures .

Initial wording:	At each visit, subjects will be asked whether they have had any UC-related events since their last visit including hospitalizations, bowel surgeries, or UC-related procedures that are not part of the protocol. The timing of the event will be collected relative to the start of treatment on Day 1 of the study through the last clinic visit. All events with timing will be recorded in the eCRFs. The underlying symptom or diagnosis should correspondingly be recorded as an AE as applicable.
Amended wording:	At each visit, subjects will be asked whether they have had any UC-related events since their last visit including hospitalizations, bowel surgeries, or UC-related procedures that are not part of the protocol. The timing of the event will be collected relative to the start of treatment on Day 1 of the study through the last clinic visit **(Follow-up Visit, 18 weeks after the last dose of study drug)**. All events with timing will be recorded in the eCRFs. The underlying symptom or diagnosis should correspondingly be recorded as an AE as applicable.

Rationale for Change: Clarification of existing text.

Change 20: Section 9.1.10 Documentation of Concurrent Medical Conditions, clarified this includes lab, ECG, or physical exam abnormalities found at Screening.

The primary change occurs in Section 9.1.10 Documentation of Concurrent Medical Conditions.

Initial wording:	Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at baseline examination. The condition (ie, diagnosis) should be described.
Amended wording:	Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at ~~baseline~~ **the Screening** examination. The condition (ie, diagnosis) should be described.

Rationale for Change: Clarification of existing text.

Change 21: Section 9.1.11 Procedures for Clinical Laboratory Samples, added that Screening labs may be repeated once at investigator discretion.
The primary change occurs in Section 9.1.11 Procedures for Clinical Laboratory Samples.
Amended wording: **All Screening laboratory tests can be repeated once at the discretion of the principal investigator.**
Rationale for Change: To allow for repeat testing at investigator discretion.

Change 22: Section 9.1.19 PK Sample Collection, clarified PK samples collection timing.	
The primary change occurs in Section 9.1.19 PK Sample Collection.	
Initial wording:	Blood samples (one 5-mL sample per scheduled time) to measure serum vedolizumab concentration will be collected into red-top Vacutainers according to the Schedule of Study Procedures in Appendix A. The actual time of sample collection will be recorded on the source document and eCRF.
Amended wording:	Blood samples (one 5-mL sample per scheduled time) to measure serum vedolizumab concentration will be collected into red-top Vacutainers according to the Schedule of Study Procedures in Appendix A. The actual **date and** time of sample collection will be recorded on the source document and eCRF. **PK samples must be collected on the same day as the visit date and prior to dosing (on the days of vedolizumab dosing).**
Rationale for Change: Clarification of existing text.	

Change 23: Section 9.1.21 Tuberculosis Screening was updated to clarify Chest X-Ray should only be performed if skin or QuantiFERON tests are indeterminate.

The primary change occurs in Section 9.1.21 Tuberculosis Screening.

Initial wording:	All subjects will complete TB screening to determine eligibility. All subjects must complete either a QuantiFERON test, a tuberculin skin test within 30 days of screening or at Screening, or chest X-ray within 3 months prior to enrollment and provide written confirmation. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 7.2.
Amended wording:	All subjects will complete TB screening to determine eligibility. All subjects must complete either a QuantiFERON test **or**~~,~~ a tuberculin skin test within 30 days of screening or at Screening~~.,~~ ~~or c~~**C**hest X-ray ~~within 3 months prior to enrollment and provide written confirmation.~~ **should be completed if high risk for TB or indeterminate skin test or QuantiFERON.** Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 7.2.

Rationale for Change: Chest X-ray should not be used as the primary screening for TB. Clarification of existing text.

Appendix A Schedule of Study Procedures. Footnote f also contains this change.

Change 24: Section 9.1.24 Documentation of Screen Failure, added rescreening criteria.	
The primary change occurs in Section 9.1.24 Documentation of Screen Failure.	
New wording:	**Subjects who fail screening may be rescreened once. Subjects undergoing rescreening must be reconsented and assigned a new subject number by IRT.**
Rationale for Change: To allow for rescreening of subjects.	

Change 25: Section 9.3.1 Screening Period, period for enrollment was clarified.

The primary change occurs in Section 9.3.1 Screening Period.

Initial wording:	Subjects will be screened within 28 days prior to Enrollment. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.24 for procedures for documenting screening failures. Procedures to be completed at Screening Visit can be found in the Schedule of Study Procedures in Appendix A.
Amended wording:	Subjects will be screened within 28 days prior to Enrollment. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. **Subjects can be enrolled at any time during the Screening period provided that all screening procedures have been completed and eligibility has been confirmed.** See Section 9.1.24 for procedures for documenting screening failures. Procedures to be completed at Screening Visit can be found in the Schedule of Study Procedures in Appendix A.

Rationale for Change: Clarification of existing text.

Change 26: Section 13.1.3 Efficacy Analysis, primary efficacy analysis was updated.

The primary change occurs in Section 13.1.3 Efficacy Analysis.

Initial wording:	All proportion-based primary, secondary and additional efficacy endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion by treatment group. The difference in proportions between treatment groups along with the 95% confidence interval will be presented. All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis. The additional efficacy endpoints of change from Baseline in CRP and fecal calprotectin will be summarized descriptively by time point and treatment group.
Amended wording:	All proportion-based primary, secondary and additional efficacy endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion by treatment group. The difference in proportions between treatment groups along with the 95% confidence interval will be presented. **The primary efficacy analyses will be based on logistic model with treatment as a factor, natural logarithm of trough concentration at Week 6 and other important covariates as explanatory variables. Odds ratio and its 95% confidence interval for treatment effect will be provided.** All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis. The additional efficacy endpoints of change from Baseline in CRP and fecal calprotectin will be summarized descriptively by time point and treatment group. **A mixed model repeated measures analysis with treatment, visit, treatment by visit as fixed effect and its baseline value as a covariate will be performed. An unstructured covariance matrix is assumed. The LS mean, p-value and 2-sided 95% confidence interval of treatment difference will be provided.**

Rationale for Change: Clarification of existing text.

Section 2.0 STUDY SUMMARY also contains this change.

Change 27: Section 13.3 Determination of Sample Size was updated to note that additional subjects may be added to account for high drop-out rates.

The primary change occurs in Section 13.3 Determination of Sample Size.

Initial wording:	The sample size was based on an estimate of precision and not on statistical power considerations. A total sample size of approximately 250 subjects enrolled to achieve approximately 100 subjects randomized at Week 6, including 50 subjects per treatment group, will be sufficient to provide 95% confidence intervals for mucosal healing rates with a half width no wider than +/-13.9%. In addition, the maximum width of the 95% confidence intervals (2-sided) for the difference in mucosal healing rates between the 2 groups will be no wider than +/-19.6%.
Amended wording:	The sample size was based on an estimate of precision and not on statistical power considerations. A total sample size of approximately 250 subjects enrolled to achieve approximately 100 subjects randomized at Week 6, including 50 subjects per treatment group, will be sufficient to provide 95% confidence intervals for mucosal healing rates with a half width no wider than +/-13.9%. In addition, the maximum width of the 95% confidence intervals (2-sided) for the difference in mucosal healing rates between the 2 groups will be no wider than +/-19.6%. **If there is a high rate of patient drop out from the study, additional patients may be added.**

Rationale for Change: Clarification of existing text.

Section 2.0 STUDY SUMMARY also contains this change.

Change 28: Appendix A, Prior UC disease treatment was added to the schedule of procedures.	
The primary change occurs in Appendix A Schedule of Study Procedures.	
Initial wording:	Medication history
Amended wording:	Medication history/**Prior UC disease treatments**
Rationale for Change: Clarification of existing text.	

Change 29: Appendix A, concomitant medications was checked at Screening.

The primary change occurs in Appendix A Schedule of Study Procedures.

New wording:

	Screening
Week	
Study Day	**-28 to -1**
Visit Window (Days):	
Concomitant medications	X

Rationale for Change: Clarification of existing text.

Change 30: Appendix A, footnote (j), PK collection was clarified.

The primary change occurs in Appendix A Schedule of Study Procedures.

Initial wording:	(j) PK samples for serum vedolizumab to be collected predose (30 minutes prior to start of infusion) prior to each dose and at Weeks 5 (all subjects) and 13 (for subjects in Dose Optimization Arm only) for determination of serum vedolizumab concentrations.
Amended wording:	(j) PK samples for serum vedolizumab **on dosing days must** ~~**to**~~ be collected predose **on the same date as the infusion** ~~(30 minutes prior to start of infusion) prior to each dose and at Weeks 5 (all subjects) and 13 (for subjects in Dose Optimization Arm only) for determination of serum vedolizumab concentrations~~ **. If the samples are not collected prior to vedolizumab dosing or not collected on the same day as the infusion, it is a significant deviation. PK samples are also collected on nondosing visits per Appendix A.**

Rationale for Change: Removed the requirement of the timing of the predose PK sample. Clarification of existing text.

Change 31: Appendix A, footnote (s), PML checklist administration was clarified.	
The primary change occurs in Appendix A Schedule of Study Procedures.	
Initial wording:	(s) PML checklist must be administered prior to vedolizumab dosing at every dosing visit.
Amended wording:	(s) PML checklist must be administered **at all visits in Appendix A and on dosing days,** prior to vedolizumab dosing ~~at every dosing visit~~.
Rationale for Change: Clarification of existing text.	

Change 32: Appendix B Responsibilities of the Investigator, added responsibility if investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

The primary change occurs in Section Appendix B Responsibilities of the Investigator.

New wording:	**If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.**

Rationale for Change: To add a new investigator responsibility per an update in the ICH guideline.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	24-Apr-2018 15:57 UTC
	Clinical Science Approval	24-Apr-2018 16:00 UTC
	Biostatistics Approval	24-Apr-2018 16:05 UTC
	Clinical Pharmacology Approval	24-Apr-2018 17:00 UTC
	Medical Affairs Approval	24-Apr-2018 18:31 UTC