



Title: A Randomized, Double-Blind, Double-Dummy, Multicenter, Active-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab IV Compared to Adalimumab SC in Subjects with Ulcerative Colitis

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PROTOCOL

A Randomized, Double-Blind, Double-Dummy, Multicenter, Active-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab IV Compared to Adalimumab SC in Subjects With Ulcerative Colitis

Efficacy and Safety of Vedolizumab IV Compared to Adalimumab SC in Subjects With Ulcerative Colitis

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Study Number: MLN0002-3026

IND Number: 009125 **EudraCT Number:** 2015-000939-33

Compound: Vedolizumab IV

Date: 26 February 2014

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

TDC 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	Americas and Europe TDC Contact
Serious adverse event and pregnancy reporting	Protected Personal Data
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

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.

Protected Personal Data



INVESTIGATOR AGREEMENT

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:

- 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/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. Takeda Development Centre Europe, Ltd. Takeda Development Center Asia, Pte. Ltd.		Compound: Vedolizumab IV	
Title of Protocol: A Randomized, Double-Blind, Double-Dummy, Multicenter, Active-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab IV Compared to Adalimumab SC in Subjects With Ulcerative Colitis		IND No.: 009125	EudraCT No.: 2015-000939-33
Study Number: MLN0002-3026		Phase: 3b	
Study Design: <p>This is a phase 3b randomized, double-blind, double-dummy, multicenter, active-controlled study to evaluate the efficacy and safety of vedolizumab compared to adalimumab over a 52-week treatment period followed by 18-week follow-up period. The study will be conducted globally and will include 658 subjects with moderately to severely active ulcerative colitis (UC).</p> <p>On Day 1, subjects who meet the inclusion criteria and who meet none of the exclusion criteria will be randomly assigned in a 1:1 ratio to double-blind medication for 50 weeks. Subjects in the vedolizumab treatment group will receive a 300 mg intravenous (IV) infusion on Day 1 and Weeks 2, 6, 14, 22, 30, 38, and 46, as well as placebo subcutaneous (SC) injection on Day 1, Week 2, and once every 2 weeks (Q2W) thereafter until Week 50.</p> <p>Subjects in the adalimumab treatment group will receive a 160 mg SC injection on Day 1 (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), 80 mg at Week 2 (two 40 mg injections in one day), then 40 mg Q2W thereafter until Week 50, as well as a placebo IV infusion at Day 1 and Weeks 2, 6, 14, 22, 30, 38, and 46. Subjects who do not respond to treatment based on the investigator's discretion should be withdrawn and treated according to standard of care.</p>			
Primary Objectives: To determine the effect of vedolizumab IV compared to adalimumab SC on clinical remission at Week 52.			
Secondary Objectives: To evaluate the effect of vedolizumab IV compared to adalimumab SC on mucosal healing at Week 52. To evaluate the effect of vedolizumab IV compared to adalimumab SC on corticosteroid-free remission at Week 52.			
Subject Population: Adult subjects 18-80 years inclusive with moderately to severely active UC			
Number of Subjects: Estimated total: 658 (329 per treatment group)		Number of Sites: Estimated total: 250 in all regions	
Dose Level(s): Vedolizumab IV 300 mg Adalimumab SC 160 mg (four 40 mg injections), 80 mg (two 40 mg injections), 40 mg		Route of Administration: Vedolizumab intravenous Adalimumab subcutaneous	

Duration of Treatment: 52-week treatment period	Period of Evaluation: The study includes a 3-week Screening Period, a 52-week Treatment Period (with last dose at Week 50), and an 18-week Follow-up Period following last dose. The duration of the study will be approximately 71 weeks. Additionally, subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.
Main Criteria for Inclusion: The subject has a diagnosis of UC established at least 6 months prior to enrollment, by clinical and endoscopic evidence and corroborated by a histopathology report. The subject has moderately to severely active UC as determined by a complete Mayo score of 6-12 with an endoscopic subscore ≥ 2 within 14 days prior to randomization. The subjects has evidence of UC extending proximal to the rectum (≥ 15 cm of involved colon). The subject has had previous treatment with tumor necrosis factor–alpha (TNF- α) antagonists without documented clinical response to treatment or the subject is naïve to TNF- α antagonist therapy but is failing current conventional treatment.	
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 checklist before the administration of study drug. 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 vedolizumab, natalizumab, efalizumab, adalimumab or rituximab.	
Main Criteria for Evaluation and Analyses: The primary endpoint for the study is proportion of subjects achieving clinical remission (defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point) at Week 52. Secondary endpoints for this study are: <ul style="list-style-type: none">• Proportion of subjects achieving mucosal healing (defined as Mayo endoscopic subscore ≤ 1 point) at Week 52.• Proportion of subjects using oral corticosteroids at Baseline who have discontinued corticosteroids and are in clinical remission at Week 52.	
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 FAS subjects with baseline concomitant oral corticosteroid use. All statistical inference will be 2-sided at a 0.05 level of significance. All proportion-based efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by randomization stratification factors. The p-values and point estimates of risk difference along with 95% CIs will be provided. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis. To control the overall Type I error rate of the primary and secondary endpoints, a hierarchical approach will be applied to the statistical testing of the secondary endpoints. The first secondary endpoint will only be tested if statistical significance is achieved with the primary endpoint, the second secondary endpoint will only be tested if statistical significance is achieved with the first secondary endpoint.	

Sample Size Justification:

A sample size of 329 subjects per group will provide 86% power at 2-sided 0.05 level of significance for Week 52 clinical remission, assuming a remission rate of 28% for vedolizumab and 18% for adalimumab; this sample size will also provide 80% power at 2-sided 0.05 level of significance for Week 52 mucosal healing, assuming a mucosal healing rate of 35% for vedolizumab and 25% for adalimumab.

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 Study-Related Responsibilities template. 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

Term	Definition
5-ASA	5-aminosalicylate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate transaminase
ADA	anti-drug antibodies
CD	Crohn's disease
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
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(ly)
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
Ig	immunoglobulin
INR	international normalized ratio
IRB	institutional review board
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test
mAb	monoclonal antibody

Term	Definition
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PTE	pretreatment event
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
QOL	quality of life
RAMP	Risk Assessment and Management Program for PML
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF- α	tumor necrosis factor- alpha
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

4.1.1 Ulcerative Colitis and Current Treatments

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal (GI) tract that includes 2 entities, namely ulcerative colitis (UC) and Crohn's disease (CD).

UC is a chronic, relapsing, inflammatory disorder of the GI tract. 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 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]. 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 such as uveitis, arthritis, ankylosis spondylitis, or primary sclerosing cholangitis may also be seen in conjunction with IBD. The diagnosis of UC is usually made by the clinical presentation and key features of the history, physical examination, in combination with laboratory 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 severe disease. Despite its use, the benefit is debatable in moderate to severely active UC [4,5].

Corticosteroids are often required for the 1/3 of patients who fail to respond to 5-ASAs [6,7]. 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 [8]. 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), which is administered by IV infusion, and adalimumab (Humira) and golimumab (Simponi), which are administered by subcutaneous (SC) injection [9-11]. 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 [12,13]. Induction of remission with infliximab occurs in only 31% to 39% of patients with UC [14] 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 [15]. 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 [9,10]. The TNF- α antagonists are also associated with a number of serious safety concerns based on their suppression of systemic immunity[9,10].

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 [16], female infertility [17], and a cumulative incidence of pouchitis of 50% at 10 years [18]. 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 called MLN0002) is a humanized immunoglobulin (Ig) G1 mAb directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to 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 [19-22]. Vedolizumab binds the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [23]. Vedolizumab has been developed as a treatment for UC and CD, which are characterized by inflammation of the GI tract.

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 several regions, including the US and European Union, for the treatment of adult patients with moderately to severely active UC or CD who have failed conventional treatment. The initial approved dosing and administration regimen consists of

300 mg vedolizumab IV infused intravenously, over approximately 30 minutes, at Weeks 0 and 2, then once every 8 weeks (Q8W) thereafter, beginning at Week 6

Previously conducted clinical studies have characterized the efficacy, safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity of vedolizumab.

4.1.2.1 Nonclinical

Nonclinical in vitro and in vivo studies have been conducted with vedolizumab and its murine homologue, Act-1. Act-1 has demonstrated clinical and histomorphologic evidence of efficacy in an animal model of IBD (cotton-top tamarins). Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted and support its clinical development. Nonclinical studies also show that vedolizumab does not antagonize $\alpha_4\beta_1$ integrin [23].

4.1.2.2 Human Experience

Single- and multiple-dose PK of vedolizumab IV have been studied in healthy subjects and in patients with moderately to severely active UC or CD and similar PK was observed. Vedolizumab exhibits target-mediated drug disposition; hence, its elimination is characterized by linear and nonlinear processes. Following IV infusion, vedolizumab serum concentrations generally fell in a biexponential fashion until approximately 1 to 10 $\mu\text{g/mL}$, with a linear total body clearance of approximately 0.157 L/day and a serum half-life of around 25 days. Thereafter, the serum concentrations fell in a nonlinear fashion. The volume of distribution for vedolizumab IV is approximately 5 L.

To date, more than 3400 subjects have received at least 1 dose of vedolizumab across all studies in the clinical development program (see current version of Investigator's Brochure [IB]). Phase 3 placebo-controlled studies enrolled 2427 subjects with UC or CD, of whom 1434 subjects were administered 300 mg of vedolizumab for induction followed by once every 4 weeks (Q4W) or Q8W for up to a total of 52 weeks and 488 subjects were administered 300 mg vedolizumab for induction only [24-26]. As of 20 July 2014, vedolizumab exposure has extended for ≥ 12 months in 1667 subjects, ≥ 24 months in 1119 subjects, ≥ 36 months in 793 subjects, and ≥ 48 months in 374 subjects.

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 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 phase and maintenance phase, respectively) compared with placebo [24-26]. The study also met important secondary endpoints, including durable clinical response, durable clinical remission, and mucosal healing at Weeks 6 and 52, and corticosteroid-free clinical remission at Week 52.

Vedolizumab has shown an acceptable safety profile based on an analysis of safety data from both completed and ongoing studies (see current version of IB). In phase 1 and 2 clinical trials (7 completed phase 1 studies in healthy subjects and 8 completed phase 1b/2 studies in UC or CD patients), there was no consistent evidence of any dose-toxicity relationships, and vedolizumab was well-tolerated up to doses of 10 mg/kg. The majority of the safety data is from 3 well-controlled, phase 3 clinical studies that evaluated the safety of vedolizumab for up to 12 months in subjects with UC (Study C13006 [52 weeks]) or CD (Studies C13007 [52 weeks] and C13011 [10 weeks]). In addition, an interim assessment of safety was performed for the ongoing, uncontrolled extension study (Study C13008) for subjects who participated in Studies C13004, C13006, C13007, or C13011 as well as de novo subjects.

Vedolizumab has shown an acceptable and consistent safety profile in clinical trials. In the pivotal phase 3 studies (C13006 and C13007), the most common ($\geq 5\%$ and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events 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 Studies C13006 and C13007, 10% of subjects were positive for antivedolizumab antibodies 16 weeks following the last dose of vedolizumab. Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment. Overall, the safety profile following long-term treatment with vedolizumab in Study C13008 is consistent with safety in the completed studies.

No cases of PML have been reported to date.

Concomitant use of corticosteroids and/or conventional immunomodulators did not appear to be associated with any increased rate of infections based on the comparative rates of infections in the phase 3 trials among subjects who had and had not received these medications.

As of 20 July 2014, a total of 14 on-study deaths (including 1 in a placebo-treated subject) were reported in the vedolizumab clinical development program, including the ongoing open-label long-term extension study C13008. The causes of death varied and detailed information can be found in the current version of the IB.

Overall, vedolizumab IV was well tolerated in clinical studies.

4.1.3 Adalimumab

Adalimumab (HUMIRA) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab binds specifically to TNF-alpha and blocks its interaction with the

p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF plays an important role in both the pathologic inflammation and the joint destruction that are hallmarks of inflammatory diseases. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

The Ulcerative colitis Long-Term Remission and maintenance with Adalimumab- (ULTRA-2) clinical trial was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of adalimumab SC in induction and maintenance of clinical remission in 494 subjects with moderate to-severe UC who received concurrent treatment with oral corticosteroids or immune-suppressants [27]. Subjects were randomly assigned to groups administered adalimumab 160 mg at Week 0, 80 mg at Week 2, and then 40 mg or placebo once every 2 weeks (Q2W). The co-primary endpoints were remission at Weeks 8 and 52. Adalimumab induced statistically significant reponse in remission rates at both Week 8 and 52. This was observed in both group of patients naïve to treatment with tumor necrosis factor-alpha (TNF- α) antagonists, among subjects who had previously received TNF- α antagonists. Adalimumab was safe and more effective than placebo in inducing and maintaining clinical remission in subjects with moderate-to-severe UC who did not have an adequate response to conventional therapy with steroids or immunosuppressants [27-29]. Current treatments have been effective for many patients with UC but have numerous limitations indicating that there is still a need for safer and more effective therapies.

4.2 Rationale for the Proposed Study

The aim of the current study is to evaluate the efficacy and safety of vedolizumab IV compared with adalimumab SC in the treatment of subjects with moderately to severely active UC. UC is a progressive inflammatory disease that usually leads to irreversible damage to the GI tract. There is a growing consensus that the ultimate goal of treatment should be to achieve complete disease control and stop progression, thus altering the natural course of UC. The most recent therapeutic outcomes have expanded beyond clinical symptom control to include steroid-free remission and mucosal healing. Clinical remission is one of the most commonly used treatment goals for subjects with UC. There are different treatment agents and combinations used currently in clinical practice to achieve this goal.

Mucosal healing is another important goal in UC therapy, it is associated with a potential improvement in quality of life, prevention of relapses, reduction in hospitalizations, reduction in disease complications and can potentially alter the natural course of the disease. Mucosal healing is assessed by colonoscopy. Mucosal inflammation manifests in its early stages with vascular congestion, erythema, edema and granularity. More advanced inflammation includes friability, spontaneous bleeding, macroscopic ulcerations, along with small or large ulcers. Many attempts have been made to define mucosal healing. The most commonly used endoscopic definition is the absence of ulcerations and inflammation. Another stricter definition of mucosal healing is the absence of friability, blood, erosions, and ulcers in all visualized segments of the gut. Additional

definitions suggest that an abnormal pattern of vascularity along with absence of the other features previously described would still be comparable with mucosal healing. There are additional challenges that need to be considered when looking at mucosal healing besides the definition, type of treatment, duration of treatment, timing of the endoscopy, and endoscopic index used. The Mayo score is the most commonly used index used to assess disease activity both in practice and clinical trials.

There are different treatment options for subjects with UC, including salicylates, steroids, immunomodulators, and biologics. These agents are used both alone and in combination. Endoscopy provides a useful way to evaluate and guide treatment response in subjects with UC. This study will evaluate mucosal healing, along with the efficacy and safety, of two current available treatments for subjects with moderately to severely active UC, namely, vedolizumab IV and adalimumab SC.

The proposed vedolizumab IV dose (300 mg at Weeks 0, 2, and 6 and Q8W, thereafter) is consistent with the approved label information [30].

The proposed adalimumab SC dose regimen (160 mg SC injection on Day 1, 80 mg SC injection at Week 2 and 40 mg Q2W thereafter) is consistent with the approved label information [10].

Pharmacogenomic analysis may be conducted to investigate the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics 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.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

- To determine the effect of vedolizumab IV compared to adalimumab SC on clinical remission at Week 52.

5.1.2 Secondary Objectives

- To evaluate the effect of vedolizumab IV compared to adalimumab SC on mucosal healing at Week 52.
- To evaluate the effect of vedolizumab IV compared to adalimumab SC on corticosteroid-free remission at Week 52.

5.1.3 Additional Objectives

- To evaluate the safety of vedolizumab IV compared to adalimumab SC.
- To evaluate the impact of vedolizumab IV on health-related quality-of-life (HRQOL) using inflammatory bowel disease questionnaire (IBDQ) at Weeks 30 and 52.

In this study, samples for pharmacogenomics will be collected and stored for possible exploratory investigation of drug response or disease. In this study, using vedolizumab, or in a set of clinical trials, if variability is seen in responsiveness to study medication and it is suspected to be attributable to gene polymorphism, pharmacogenomics analyses may be conducted to explore gene polymorphism relationships, as indicated by the observations.

5.2 Endpoints

5.2.1 Primary Endpoints

- Proportion of subjects achieving clinical remission (defined as a complete Mayo score of ≤ 2 points and no individual subscore >1 point) at Week 52.

5.2.2 Secondary Endpoints

- Proportion of subjects achieving mucosal healing (defined as Mayo endoscopic subscore ≤ 1 point) at Week 52.
- Proportion of subjects using oral corticosteroids at Baseline who have discontinued corticosteroids and are in clinical remission at Week 52.

5.2.3 Additional Endpoints

- Proportion of subjects achieving clinical response (defined as a reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline [or a partial Mayo score of ≥ 2 points and $\geq 25\%$ from baseline, if the complete Mayo score was not performed at the visit] with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point) at Week 52.
- Proportion of subjects achieving clinical remission (defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point) at Week 14.
- Proportion of subjects with rectal bleeding subscore indicative of mild disease (≤ 1) at Week 52.
- Proportion of subjects with a Physician's Global Assessment (PGA) subscore indicative of mild disease (≤ 1) at Week 52.
- Proportion of subjects with stool frequency subscore indicative of mild disease (≤ 1) at Week 52.
- Proportion of subjects with complete Mayo score of ≤ 2 points and no individual subscore > 1 point where rectal bleeding subscore of 0 and endoscopy subscore of 0 at Week 52.
- Proportion of subjects with endoscopy subscore of 0, rectal bleeding subscore of 0, and stool frequency subscore decreases or no change from Baseline at Week 52.
- Proportion of subjects with endoscopy subscore ≤ 1 , rectal bleeding subscore of 0, and stool frequency subscore of 0 at Week 52.
- Proportion of subjects with endoscopy subscore ≤ 1 , rectal bleeding subscore of 0, and stool frequency subscore ≤ 1 at Week 52.
- Proportion of subjects with endoscopy subscore ≤ 1 , rectal bleeding subscore of 0, stool frequency subscore decreases or no change from Baseline, and total score (sum of these 3) ≤ 1 at Week 52.
- Proportion of subjects with IBDQ score change of ≥ 16 points from Baseline to Week 52.
- Proportion of subjects reaching clinical remission based on IBDQ score > 170 at Week 52.
- Change in oral corticosteroid use from Baseline to Week 52.
- Proportion of subjects using oral corticosteroids at Baseline who have discontinued corticosteroids and are in clinical remission at Week 14.
- Time to major UC-related events (eg, hospitalizations, colectomies, and procedures).
- Change in fecal calprotectin concentrations from Baseline to Weeks 14, 30, and 52.
- Proportion of subjects with a change in histology from baseline to Week 52.

- Safety for maintenance therapy 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), serious adverse events (SAEs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and results of 12 lead electrocardiograms (ECGs).

6.0 STUDY DESIGN AND DESCRIPTION.

6.1 Study Design

This is a phase 3b randomized, double-blind, double-dummy, multicenter, active-controlled study to evaluate the efficacy and safety of vedolizumab compared to adalimumab over a 52-week treatment period. The study will be conducted globally and will include 658 subjects (329 per treatment group) with moderately to severely active UC.

The study consists of a 3-week Screening Period, a 52-week Treatment Period (with last dose at Week 50), and an 18-week Follow-up Period following last dose. Additionally, subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug. The duration of the study will be approximately 71 weeks for all subjects.

Subjects who have moderately to severely active UC, defined as Mayo score 6-12 and endoscopic subscore ≥ 2 both anti-TNF- α naïve and failures, will be screened. Previous use of TNF- α therapy other than adalimumab will be permitted. Subjects who are naïve to TNF- α antagonist treatment and those who failed TNF- α therapy will be allowed to enroll; however, the proportion of TNF- α antagonist naïve subjects shall not exceed approximately 50% of the total number of subjects enrolled into the study.

On Day 1, subjects who meet the inclusion criteria and who meet none of the exclusion criteria will undergo baseline evaluations and be randomly assigned in a 1:1 ratio to double-blind medication for 50 weeks. Randomization will be stratified by:

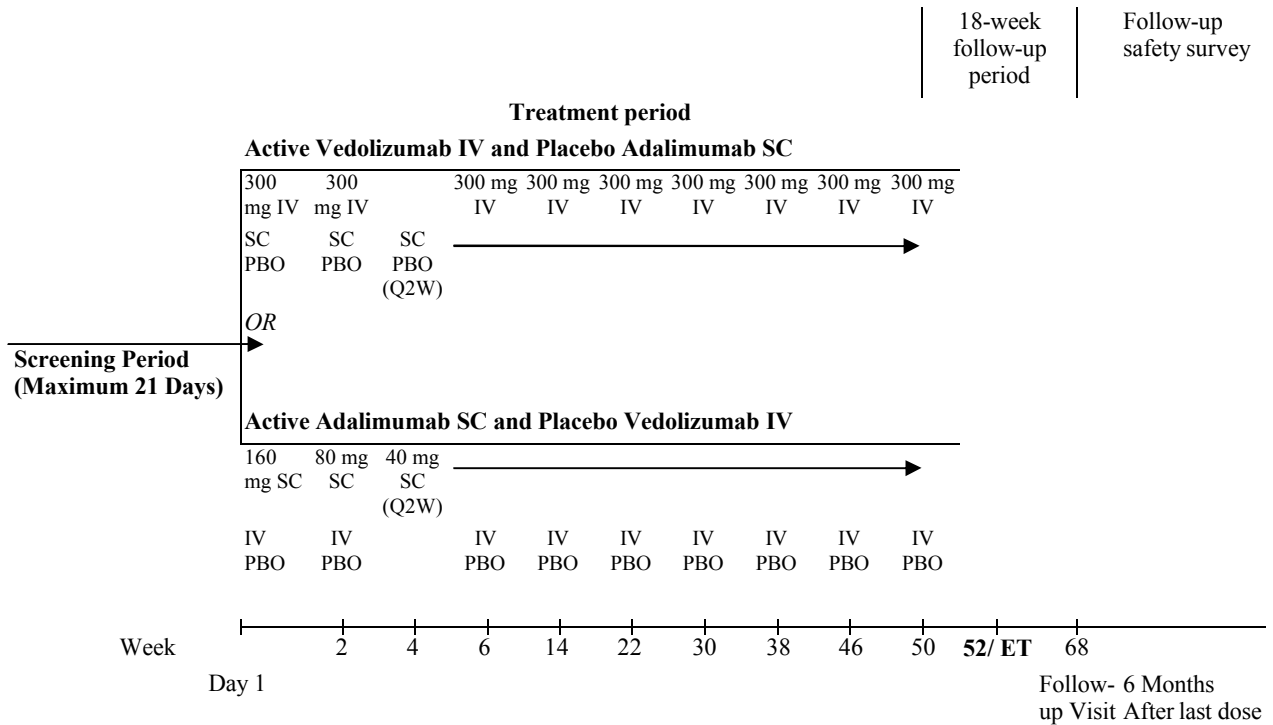
- Concomitant use of oral corticosteroids.
- Previous failure of TNF- α antagonist therapy or naïve to TNF- α antagonist therapy.

Subjects in the vedolizumab treatment group will receive a 300 mg IV infusion on Day 1 and Weeks 2, 6, 14, 22, 30, 38, and 46, as well as placebo SC injection on Day 1, Week 2, and Q2W thereafter until Week 50.

Subjects in the adalimumab treatment group will receive a 160 mg SC injection on Day 1 (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), 80 mg at Week 2 (two 40 mg injections in one day), then 40 mg Q2W thereafter until Week 50, as well as a placebo IV infusion at Day 1 and Weeks 2, 6, 14, 22, 30, 38, and 46. Subjects who do not respond to treatment based on the investigator's discretion should be withdrawn and treated according to standard of care. After the Week 52 or End of Study Visit, all subjects will have a Follow-Up Visit, approximately 18 weeks (approximately 5 half-lives for vedolizumab) after the last dose of study drug.

A schematic of the study design is included as [Figure 6.a](#). A schedule of assessments is listed in [Appendix A](#).

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

The aim of the current study is to evaluate the efficacy and safety of vedolizumab IV compared with adalimumab SC in the treatment of subjects with moderately to severely active UC. Clinical remission is one of the treatment goals for subjects with UC. There are different treatment agents and combinations used currently in clinical practice to achieve this goal.

Vedolizumab has a unique, highly gut-selective immunomodulatory mechanism of action that provides the basis for its development as a treatment for UC. In a pivotal phase 3 clinical trial, vedolizumab IV was effective for induction and maintenance therapy in subjects with UC [24].

The primary endpoint evaluated in this study will be clinical remission at Week 52. Because UC is a progressive disease with long-term structural and functional complications, the duration of the study is proposed as 52 weeks to provide a long-term comparison of the efficacy data. Other secondary endpoints, will include mucosal healing, corticosteroid-free remission, and additional endpoints will also be patient-reported outcomes (PROs) and AEs. Mucosal healing has been associated with better outcomes for UC patients, such as reduction in colectomies and less treatment failure [27]. Corticosteroid use is associated with inadequate disease control and can lead in some subjects to adverse reactions; therefore, minimizing corticosteroid use as a treatment goal will benefit subjects [28]. PROs provide a complement to the clinical data collected as they focus on the subject’s assessment of their disease.

Subjects will receive vedolizumab IV 300 mg on Day 1, Weeks 2 and 6, and Q8W thereafter until Week 46 or adalimumab 160 mg SC on Day 1, 80 mg SC at Week 2 and 40 mg SC Q2W thereafter until Week 50, and subjects in each arm will receive matching placebo injections or infusions. The initial dosing recommendations in the dosing regiment for both vedolizumab IV and adalimumab SC follows the approved labels [30] [10].

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, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has a diagnosis of UC established at least 6 months prior to screening by clinical and endoscopic evidence and corroborated by a histopathology report.
4. The subject is male or female and aged 18 to 80 years, inclusive.
5. The subject has moderately to severely active UC as determined by a Mayo score of 6 to 12 with an endoscopic subscore ≥ 2 within 14 days prior to the randomization.
6. The subject has evidence of UC proximal to the rectum (≥ 15 cm of involved colon).
7. The subject with extensive colitis (up to the hepatic flexure) or pancolitis of >8 years duration or left-sided colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (may be performed during the Screening Period).
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 previous treatment with TNF- α antagonists without documented clinical response to treatment or the subject is naïve to TNF- α antagonist therapy but is failing current treatment.
10. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.
11. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

*Definitions and acceptable methods of contraception are defined in Section 9.1.12 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.13 Pregnancy.

7.2 Exclusion Criteria

The exclusion criteria are divided into 3 categories: gastrointestinal exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Any subject who meets any of the following criteria will not qualify for entry into the study:

Gastrointestinal Exclusion Criteria

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, ischaemic 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 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 the screening (whichever is longer).
7. The subject has previously received natalizumab, efalizumab, adalimumab, or rituximab.
8. The subject has previously received 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.

Infectious Disease Exclusion Criteria

1. The subject has evidence of an active infection during the Screening Period.
2. The subject has evidence of, or treatment for, C. difficile infection or other intestinal pathogen within 28 days prior to the first dose of study drug.
3. The subject has chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
4. The subject has active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:
 - a) History of TB,

- b) A diagnostic TB test performed within 30 days of enrollment that is positive, defined as:
 - Positive QuantiFERON[®] test or 2 successive indeterminate QuantiFERON tests OR
 - A TB skin test reaction ≥ 10 mm (≥ 5 mm in subjects receiving the equivalent of >15 mg/day prednisone)
 - c) Chest X-ray within 3 months of enrollment in which active or latent pulmonary TB cannot be excluded.
5. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus (HIV) infection, organ transplantation).
 6. The subject has any live vaccination within 30 days prior to screening or is planning to receive live vaccination during participation in the study.
 7. The subject has a clinically significant infection (eg, pneumonia, pyelonephritis) within 30 days prior to screening, or ongoing chronic infection.
 8. 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.

General Exclusion Criteria

1. The subject has a history of hypersensitivity or allergies to vedolizumab or adalimumab.
2. The subject has any unstable or uncontrolled cardiovascular, 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.
3. The subject has history of lupus or lupus-related conditions.
4. 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.
5. 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.
6. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease.
7. The subject has a positive PML subjective symptom checklist prior to the administration of the first dose of study drug.

8. The subject has any of the following laboratory abnormalities during the Screening Period:
 - Hemoglobin <8 g/dL.
 - White blood cells (WBC) < 3×10^9 /L.
 - Lymphocyte < 0.5×10^9 /L.
 - Platelet count < 100×10^9 /L or > 1200×10^9 /L.
 - ALT or AST > $3 \times$ upper limit of normal (ULN).
 - Alkaline phosphatase > $3 \times$ ULN.
 - Serum creatinine > $2 \times$ ULN.
9. 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.
10. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
11. The subject is unable to attend all the study visits or comply with study procedures.
12. The subject is required to take excluded medications listed in Section 7.3.
13. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
14. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
15. The subject is an immediate family member, study site employee, or is in a dependant 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 Excluded Medications

The following medications are excluded from the study:

- Any treatment for UC other than those listed in Section 7.3.1 (either approved or investigational).
- All live vaccines, during study treatment and for at least 6 months after the last dose of study drug.
- Either approved or investigational biological agents for the treatment of non-IBD conditions,
- Chronic nonsteroidal anti-inflammatory (NSAID) use. (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc. and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted.)

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

7.3.1 Permitted Medications

The following medications are permitted during the study:

- Topical (rectal) corticosteroid enemas/suppositories.
- The subject may be receiving a therapeutic dose of the following agents:
 - Oral 5-ASA compounds with a dose stable at least 2 weeks prior to screening.
 - Oral corticosteroid therapy (prednisone at a stable dose ≤ 30 mg/day, or equivalent steroid) provided that the dose has been stable for at least 4 weeks prior to screening, if corticosteroids have been just initiated, or 2 weeks prior to screening if corticosteroids are being tapered.
 - Probiotics, provided that the dose has been stable for at least 2 weeks prior to screening.
 - Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
 - Azathioprine, 6-mercaptopurine, or methotrexate, provided that the dose has been stable for 8 weeks immediately prior to screening.

Any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC symptoms (other than anti-diarrheals for control of chronic diarrhea) is considered a rescue medication. Administration of a rescue medication constitutes treatment failure (ie, lack of efficacy) and the subject should be withdrawn from the study according to Section 7.4.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.20.

1. Pretreatment event (PTE) or adverse event (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 (LFT) 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 9.1.9), if the following circumstances occur at any time during study medication treatment:

- ALT or AST $> 8 \times$ upper limit of normal (ULN), or
- ALT or AST $> 5 \times$ ULN and persists for more than 2 weeks, or

- ALT or AST $>3 \times$ ULN in conjunction with elevated total bilirubin $>2 \times$ ULN or international normalized ratio (INR) >1.5 , or
 - ALT or AST $>3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($>5\%$).
2. Leukopenia or Lymphopenia. WBC and lymphocyte counts will be monitored for all subjects. Azathioprine, 6-mercaptopurine, or methotrexate, if applicable, should be discontinued and the dose of study drug held for an absolute lymphocyte count $<0.5 \times 10^9/L$ at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of study drug can be administered only if the absolute lymphocyte count is $\geq 0.5 \times 10^9/L$. If the absolute lymphocyte count remains $<0.5 \times 10^9/L$, study drug should be discontinued and the subject withdrawn from the study.
 3. 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.
 4. 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.
 5. 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).
 6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
 7. 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 9.1.13.
 8. 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.
 9. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 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 7.4. 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

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the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

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

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Vedolizumab IV or Matching Placebo

The study sites will be supplied by the sponsor with the following 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 formulation for reconstitution using sterile water. Each vial will be packaged in an appropriately labeled single vial carton.

The placebo infusion will be 250 mL of 0.9% sodium chloride. For both active vedolizumab and placebo infusions, the investigational pharmacist or designee will mask the IV bags after preparation in order to maintain the study blind.

All infusions will be administered IV over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on study observations. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and one hour after each subsequent infusion. in a room where appropriate treatment for infusion-related reactions is available. The subject should be considered clinically stable by the investigator or designee prior to discharge.

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

8.1.1.2 Adalimumab SC or Matching Placebo

The study sites will be supplied by the sponsor with the following medication in a blinded manner: adalimumab 40 mg/SC placebo in pre-filled syringes.

Each carton will have a single-panel or multilingual booklet label that will contain, but will not be limited to the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, medication identification number, subject information, caution statement, directions for use, and storage conditions.

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 transported and

stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Vedolizumab IV, adalimumab SC, and SC placebo must be stored at 2°C to 8°C (36°F to 46°F), protected from light. Do not freeze adalimumab SC and do not use adalimumab SC if frozen.

The dose and regimen for the treatment groups is summarized in [Table 8.a](#).

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
		Active	Placebo
A	Vedolizumab IV 300 mg/placebo	Vedolizumab IV 300 mg Day 1, Weeks 2, 6, 14, 22, 30, 38, and 46 (Q8W)	Placebo for Adalimumab SC 160 mg Day 1, 80 mg Week 2, 40 mg Weeks 4 to 50 (Q2W)
B	Adalimumab SC 160 mg, 80 mg, 40 mg/placebo	Adalimumab SC 160 mg Day 1, 80 mg Week 2, 40 mg Weeks 4 to 50 (Q2W)	Placebo for Vedolizumab IV 300 mg Day 1, Weeks 2, 6, 14, 22, 30, 38, and 46 (Q8W)

Dosing regimen follow approved vedolizumab IV and adalimumab SC labels [10,30].

8.1.3 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.

Serious 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 receive treatment according to study schedule.

The investigator or investigator's designee will access the interactive voice response system (IVRS)/ interactive web response system (IWRS) at Screening to obtain the subject study number. The investigator or the investigator's designee will utilize the IVRS/IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication identification (ID) number of the investigational drug to be dispensed will then be

provided by the IVRS/IWRS by email notification to the unblinded site pharmacist/nurse. To maintain the blind the IVRS/IWRS will ensure the investigator or designee is unaware of a medication ID assigned to the subject. If sponsor-supplied drug (vials or pre-filled syringes) is lost or damaged, the unblinded site staff can request a replacement from IVRS/IWRS. Refer to IVRS/IWRS manual provided separately.

At subsequent drug-dispensing visits, the investigator or designee will again contact the IVRS/IWRS to request additional investigational drug for a subject. The medication ID number of the investigational drug to be dispensed will be provided by the IVRS/IWRS to the unblinded site staff only.

8.3 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IVRS/IWRS. All subjects and study personnel except for those directly involved with study drug preparation will be blinded to study drug assignment for the entire study

8.4 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IVRS/IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

8.5 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 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, 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 IVRS/IWRS. 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 Medication 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 IVRS/IWRS 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 300 mg, adalimumab SC 40 mg) 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.

All study drug that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

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.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

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.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned 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

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting a blood sample for Pharmacogenomic Research for this study. The provision of consent to collect and analyze the pharmacogenomic sample is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, 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 9.1.8).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped within 30 days prior to signing of informed consent.

In addition, all prior biologic medication history for the treatment of ulcerative colitis disease with the reason for discontinuation is to be collected for subjects where possible.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of investigational drug) 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 should assess clinically significant changes from the assessment prior to first dose examination.

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9.1.4 Weight, Height

A subject should have weight and height measured while 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.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (bpm). On dosing days, vital signs are taken predose.

9.1.6 Primary Efficacy Measurement

Primary and secondary efficacy assessments will be based on Mayo scores. A complete Mayo score will be obtained within 14 days prior to randomization to determine eligibility. Results obtained during Screening will be the Baseline complete Mayo score. Sigmoidoscopy will be done during screening, Weeks 14 and 52 (or ET visit), and complete Mayo score will be calculated for these visits. The baseline complete Mayo score will be used for the comparison with the Week 14 and 52 complete Mayo score to determine response and remission at Weeks 14 and 52.

A partial Mayo score will be derived for the visits at which endoscopy will not be performed. These scores will be used to determine clinical response or disease worsening during the study.

The Mayo endoscopic subscore determination will be based upon central readings to eliminate assessment bias. Refer to [Appendix E](#) for information on the Mayo Scoring System.

9.1.6.1 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. Diary entries will be made daily by the subject through a validated electronic system. Entries should be reviewed and monitored by the study staff.

9.1.6.2 Flexible Sigmoidoscopy and Biopsy

Flexible sigmoidoscopy will be performed during screening, Week 14, and Week 52 (or ET visit). Results of sigmoidoscopy will be used for calculation of complete Mayo score at these visits. On the days sigmoidoscopy is done biopsy samples will be collected from all subjects to evaluate changes in histology.

Additional information regarding the sigmoidoscopy requirements and central reader assessments can be found in the Study Manual.

9.1.7 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 end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.8 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 screening examination. The condition (ie, diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 25 mL, and the approximate total volume of blood for the study is 165 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

The clinical laboratory tests to be conducted during the study are summarized in [Table 9.a](#). The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST $>3 \times \text{ULN}$, 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 48-72 hours after the abnormality was noted.

(Please refer to [Section 7.4](#) 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 $>3 \times \text{ULN}$ in conjunction with total bilirubin $>2 \times \text{ULN}$.)

If the ALT or AST remains elevated $>3 \times \text{ULN}$ 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)

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	Alanine aminotransferase	Bilirubin
White blood cells	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	Amylase	Ketones
Platelets	Aspartate aminotransferase	Leukocyte esterase
PT/INR	Bicarbonate	Nitrite
	Calcium	pH
	Chloride	Protein
	Total protein	Specific gravity
	Creatinine	Microscopic (to be obtained in the event of positive leukocyte esterase or blood, will include WBCs, RBCs, and cast[s])
	Blood urea nitrogen	
	Creatine kinase	
	GGT	
	Glucose	
	Lipase	
	Magnesium	
	Phosphorus	
	Potassium	
	Sodium	
	Total and direct bilirubin	
	Total protein	
	Uric acid	
Other:		
Serum	Urine	Stool
CRP	Urine pregnancy hCG	Fecal calprotectin
Hepatitis panel, including HBsAg and anti-HCV	(female subjects of childbearing potential)	<i>C. Difficile</i> test
ADA		
Quantiferon		
Pharmacogenomic sample		
Follicle-stimulating hormone (FSH)		
If menopause is suspected:		
Beta hCG (female subjects of childbearing potential)		

CRP=C-reactive protein, FSH=follicle-stimulating hormone, GGT= γ -Glutamyl transferase, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells

9.1.10 Fecal Calprotectin Sample Collection

A stool sample will be collected on Day 1, Weeks 14, 30, and 52 (or ET Visit) for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity.

9.1.11 Stool Sample

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 patient becomes symptomatic, including worsening or return of disease activity.

9.1.12 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (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).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):	Intrauterine devices (IUDs):	#Hormonal contraceptives:
<ul style="list-style-type: none">• Male condom PLUS spermicide.• Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.• Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.	<ul style="list-style-type: none">• Copper T PLUS condom or spermicide.• #Progesterone T PLUS condom or spermicide.	<ul style="list-style-type: none">• Implants.• Hormone shot/injection.• Combined pill.• Minipill.• Patch.• Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable 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.

During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures ([Appendix A](#)). In addition to a negative serum hCG pregnancy test at screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication as close as possible and prior to first dose of study medication, preferably on the same day.

In addition, male subjects must be advised not to donate sperm from signing of informed consent to 18 weeks after the last dose of study medication.

9.1.13 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. 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 active study medication, eg, after Visit on 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.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

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 (blinded or unblinded, as applicable).

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

9.1.14 ECG Procedure

A standard 12-lead ECG will be recorded. 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.

9.1.15 Pharmacogenomic Sample Collection

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

Two whole blood samples (3 mL per sample) for DNA isolation will be collected into plastic K2 ethylenediamine-tetraacetic acid (EDTA) spray coated tubes before dosing on Day 1 from each subject in the study, and stored under frozen conditions.

Two whole blood samples (2.5 mL per sample) for RNA isolation will be collected into PAXgene™ tubes before dosing on Day 1 from each subject in the study. Samples should be collected on ice and stored in the 2-8°C refrigerator for a maximum of 3 days and samples will be frozen at -20°C or lower and shipped separately on dry ice prior to RNA extraction and storage at -20°C or lower.

Ileocolonoscopy tissue samples that are collected may also be used to look for changes in mRNA expression patterns associated with disease or response to therapy. The specimens should be placed into the formalin-fixed bottle prefilled with 10% neutral-buffered formalin and the second specimen should be placed into the RNA later bottle prefilled with RNA later solution.

DNA and RNA form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets. DNA and RNA 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 the study drug.
- 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 medications, and for improving the efficiency, design and study methods of future research studies.

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. Please refer to the Study Manual for information on sample collection and preparation.

The samples will be stored for no longer than 15 years after completion of the study. 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 key-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 investigational drug or related drugs.

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

9.1.16 Immunogenicity Sample Collection

Blood specimens for the assessment of ADA will be collected as shown in the schedule of events, for both vedolizumab and adalimumab. ADA and its impact may be assessed at a later time point if warranted by the data. Please refer to the Study Manual for information on sample collection and preparation.

9.1.17 Tuberculosis Screening

All subjects will complete TB screening to determine eligibility. All subjects must complete a diagnostic test during screening either a QuantiFERON[®] test or a tuberculin skin test. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 7.2.

9.1.18 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 intravenous 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 Minimization for PML (RAMP). The symptoms from a positive PML checklist will be recorded as an AE. Additional information and tools for the RAMP can be found in the Study Manual.

9.1.19 Patient Reported Outcome Measures

Subjects will complete the IBDQ questionnaire at the time points specified in the schedule of events.

9.1.19.1 Inflammatory Bowel Disease Questionnaire

The IBDQ is a valid and reliable [31] instrument used to assess quality of life in adult patients with IBD. It includes 32 questions on 4 domains of health-related quality of life (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 [32]. A total IBDQ score ≥ 170 is associated with clinical remission [32,33].

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this visit, the investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of screen failure.

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.
- Study termination.
- Other.

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

9.1.21 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

Randomization will be stratified by:

- Concomitant use of oral corticosteroids.
- Previous failure of TNF α antagonist therapy or naïve to TNF α antagonist therapy.

9.2 Monitoring Subject Treatment Compliance

If a subject is persistently noncompliant with the study medication, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.2.1 Schedule of Observations and Procedures

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

9.2.2 Screening

Subjects will be screened within 21 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.20 for procedures for documenting screening failures.

Procedures to be completed at Screening can be found in the schedule of events.

9.2.3 Randomization

Randomization will take place on Day 1. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria, the subject should be randomized using the IVRS/IWRS, as described in Section 8.2. Subjects will be instructed on when the first dose of investigational drug will be given as described in Section 6.1. The procedure for documenting screening failures is provided in Section 9.1.20.

9.2.4 Final Visit or Early Termination

The Final Visit will be performed on Week 52 or at the Early Termination Visit.

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

9.2.5 Follow-up

Follow-up will begin after last dose of study drug and will continue for 18 weeks thereafter.

Additionally, upon completion of or early termination from the study, all subjects will participate in a LTFU safety questionnaire. The questionnaire will be administered by telephone at 6 months from the last dose of study drug.

9.2.6 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

Subject to applicable laws and feasibility, access to the study medication may be available to individual subjects for whom no standard therapy exists, and the subject is at risk of significant morbidity or mortality. The investigator should contact the medical monitor to determine if access is possible.

9.3 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described. After extraction and purification, 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 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.

In this study, ileocolonoscopy tissue samples 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 tissue samples will be sent to a central laboratory that serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected. 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 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 ileocolonoscopy tissue 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. In addition, drug-device AEs related to quality or malfunction will be collected.

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 re-test 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

A Special Interest Adverse Event (serious or non-serious) is one 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.

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 one 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 AE collection: AEs must be collected from start of study medication administration.
- End of AE collection: AEs must be collected for 18 weeks following the last dose of study medication.

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 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication. Routine collection of AEs will continue until 18 weeks after last dose.

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. Non-serious 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.
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.

IBDQ is patient reported instrument used to measure health related quality of life in this study. It 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 Adverse Event Collection Involving Medically Anticipated Clinical Events

Ulcerative colitis is associated with certain characteristic signs and symptoms including diarrhea, rectal bleeding, and abdominal pain that may be present at baseline and persist or fluctuate based on the individual subject's disease history during the course of the study. These signs and symptoms will not be collected as AEs.

Exacerbations of disease activity (eg, increase in the daily amount of rectal bleeding or abdominal pain beyond the subject's normal fluctuation, new signs and symptoms of UC) will be collected as AEs and reported according to regulatory reporting requirements.

Extra-intestinal manifestations of the subject's disease (eg, arthralgia, arthritis, uveitis) that develop or worsen during the study are considered AEs.

10.2.1.4 Special Interest AE Reporting

If this special interest AE occurs during the Treatment Period or the Follow-up Period is considered to be clinically significant based on the criteria below, it should be recorded in the special interest AE eCRF or an SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

Injection and/or Infusion Site Reactions and Hypersensitivity

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; 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 professional 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 one hour after each subsequent infusion.

Subjects should 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, injection-site reactions or infusion-related reactions) to study medication. If signs or symptoms of infusion-related reaction are observed during the administration of study, 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) at the discretion of the investigator. Subjects with severe or serious administration-related reactions (eg, stridor, angioedema, life-threatening change in vital signs) 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.

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 7.4.

Malignancies

All cases of malignancies that are detected during the study will be reported as AEs. Local medical practices for the management of malignancies 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.

Other

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

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 eCRF or Form must be completed, in English, 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.

The SAE eCRF should be completed within 24 hours of first onset or notification of the event. However as a back-up, if required, the SAE Form should be completed and reported to Takeda Pharmacovigilance or designee within 24 hours to the attention of the contact listed in Section 1.1.

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 Liver Function Tests

If a subject is noted to have ALT or AST elevated $>3 \times \text{ULN}$ 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 $>3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$ 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 9.1.9 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 Monitoring Committee will be used in this study.

11.1 Adjudication Committee

A PML Independent Adjudication Committee (IAC) will be implemented 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 Minimization Action Plan for PML (RAMP Program)

Natalizumab (TYSABRI), another integrin receptor antagonist, has been associated with progressive multifocal leukoencephalopathy (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 [34,35]. Natalizumab is a pan- α_4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1 [36,37]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [23] 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, the sponsor, with input from renowned PML experts, has developed a Risk Minimization Action Plan for PML, the RAMP. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the 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 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 will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. An IAC has been stabled 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. Adjudication Committee

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 (WHO) Drug Dictionary.

12.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor 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. Reasons for significant corrections should additionally be included.

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.

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 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 unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review meeting will be conducted prior to unblinding of subject's treatment assignment. 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 dose of study drug. Subjects in this set will be analyzed according to the treatment they were randomized to receive.

The Per-Protocol (PP) Population is a subset of the intent-to-treat population. The PP Population consists of all subjects who do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects for the PP Population dataset will be made prior to the unblinding of the study. Analyses using the per-protocol population may be provided as a sensitivity analysis.

The Safety Analysis Set will include all subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment they actually received.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall based on all randomized subjects. Additional summaries will be provided for the Full Analysis Set as appropriate. For continuous variables, summary statistics (non-missing 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 term.

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 FAS subjects with baseline concomitant oral corticosteroid use. All statistical inference will be 2-sided at a 0.05 level of significance.

All proportion-based efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by randomization stratification factors. The p-values and point estimates of risk

difference along with 95% CIs will be provided. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

To control the overall Type I error rate of the primary and secondary endpoints, a hierarchical approach will be applied to the statistical testing of the secondary endpoints. The first secondary endpoint, proportion of subject achieving mucosal healing at Week 52, will only be tested if statistical significance is achieved with the primary endpoint. The second secondary endpoint, proportion of subjects using oral corticosteroids at Baseline who have discontinued corticosteroids and in clinical remission at Week 52, will only be tested if statistical significance is achieved with the first secondary endpoint.

Testing of the additional efficacy endpoints will not be multiplicity-controlled. The following analyses will be performed on endpoints that are not proportion-based:

- Change from Baseline in oral corticosteroid use will be summarized for FAS subjects with baseline concomitant oral corticosteroids use, and tested using Wilcoxon rank-sum test.
- Change from Baseline in fecal calprotectin will be analyzed with an analysis of covariance model with treatment and randomization stratification factors as factors and Baseline fecal calprotectin as a covariate.

13.1.4 Other Analyses

Time to UC-related hospitalizations, colectomies, and UC-related hospitalizations procedures will be analyzed using a Wei-Lin-Weissfeld (WLW) Cox-regression model with treatment group, baseline complete Mayo score, randomization stratum, and geographic region as independent variables. For each of the components, the treatment groups will be compared by log-rank tests, with Kaplan-Meier estimates of Month 6 and Month 12 event rates presented.

13.1.5 Safety Analysis

Safety analysis will be performed using the Safety Analysis Set. 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, injection site 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 Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, High Level Term, and Preferred Term overall, by severity, and by relationship to study drug 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 treatment group. Subjects with markedly abnormal values for laboratory tests and vital signs will be tabulated.

The shift in ECG interpretation from baseline will be summarized by treatment group. Physical examination findings and PML checklist data will be presented in data listings.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

A sample size of 329 subjects per group will provide 86% power at 2-sided 0.05 level of significance for Week 52 clinical remission, assuming a remission rate of 28% for vedolizumab and 18% for adalimumab; this sample size will also provide 80% power at 2-sided 0.05 level of significance for Week 52 mucosal healing, assuming a mucosal healing rate of 35% for vedolizumab and 25% for adalimumab.

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 (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), 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. A Protocol Deviation Form should be completed by the site and signed 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 [drug/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.

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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 [e]CRF).

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.

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.

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 Americas 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

Study Day/Week:	Screen- ing	Treatment week															Final Visit or Early Termination Visit Week 52(b)	Follow-up visit week 68
	Days 21 to -1	Day 1 (a)	2	4	6	8, 10, 12	14	16, 18, 20	22	24, 26, 28	30	32, 34, 36	38	40, 42, 44	46	48, 50		
Visit Windows (Days):		± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Informed consent	X																	
Inclusion/exclusion criteria	X	X (a)																
Demographics and medical history	X																	
Concurrent medical conditions	X																	
Medication history	X																	
Physical examination	X	X (a)	X	X	X		X		X		X		X		X		X	X
Vital signs (b)	X	X (a)	X	X	X		X		X		X		X		X		X	X
Weight and height	X																	
Flexible sigmoidoscopy (c)	X						X										X	
Mayo score	X						X										X	
Partial mayo score		X	X	X	X				X		X		X		X			
Patient diary	X	X (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory testing (d)	X	X (a)			X		X				X				X		X	X
ADA testing (e)		X (a)			X		X		X		X		X				X	X
HIV/Hepatitis panel	X																	
Tuberculosis screening (f)	X																	
Pharmacogenomic DNA and RNA sample collection		X (a)																
Serum pregnancy test (g)	X																	
Urine pregnancy test (g)		X (a)	X	X	X	X (g)	X	X (g)	X	X (g)	X	X (g)	X	X (g)	X	X (g)	X	X

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Study Day/Week:	Screen- ing	Treatment week															Final Visit or Early Termination Visit Week 52(b)	Follow-up visit week 68	
	Days 21 to -1	Day 1 (a)	2	4	6	8, 10, 12	14	16, 18, 20	22	24, 26, 28	30	32, 34, 36	38	40, 42, 44	46	48, 50			
Visit Windows (Days):		± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
IBDQ		X (a)									X							X	
ECG	X																	X	
Stool sample for C. difficile	X																		
Stool sample for calprotectin		X					X				X							X	
PML checklist	X	X (a)	X		X		X		X		X		X		X	X	X	X	X
SC dosing (adalimumab or placebo)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IV dosing (vedolizumab or placebo)		X	X		X		X		X		X		X		X				
PTE assessment (h)	X	X																	
Adverse Events (i)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications (j)		X (a)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(a) Assessments to be completed predose.

(b) Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (bpm). On dosing days, vital signs are taken predose.

(c) Biopsies to be collected at Screening and Week 14 and 52. 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.

(d) Blood sample obtained during screening should be in fasted state

(e) Blood samples for the ADA (anti-drug antibodies against vedolizumab or adalimumab) assessment will be collected from all subjects at Day 1 and Weeks 6, 30, 38, 52, and 68. On dosing days, blood samples must be taken pre-dose.

(f) Assessed by QuantiFERON[®] test, A TB skin test reaction or chest X-ray within 3 months of enrollment

(g) Women of childbearing potential only. Urine pregnancy test should be done before every IV infusion and on Weeks 10, 18, 26, 34, 42, and 50.

(h) PTEs will be captured immediately following the signing of the informed consent at the Screening Visit, up until the first dose of study drug. Collection of AEs will begin following first dose of study drug and will continue through Week 68/Final Safety Visit.

(i) Collection of all SAEs will begin once the informed consent is signed and will continue through Week 68/Final Safety Visit.

(j) Monitoring of concomitant medications will begin at signing of the informed consent.

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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 from 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:

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 56, 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.

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. 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. 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date <small>(dd-MMM-yyyy HH:mm)</small>
Protected Personal Data	Biostatistics Approval	26-Feb-2015 22:37
	Clinical Science Approval	26-Feb-2015 22:47
	Clinical Science Approval	27-Feb-2015 07:03