



Title: An Open-Label Phase 3b Study to Assess Mucosal Healing in Subjects With Moderately to Severely Active Crohn's Disease Treated With Vedolizumab IV

NCT Number: NCT02425111

Protocol Approve Date: 28 November 2016

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**An Open-Label Phase 3b Study to Assess Mucosal Healing in Subjects With Moderately to Severely Active Crohn's Disease Treated With Vedolizumab IV**

**Effect of Vedolizumab IV on Mucosal Healing in Crohn's Disease**

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**Study Number:** MLN0002-3028

**IND Number:** 009125      **EudraCT Number:** 2014-003509-13

**Compound:** Vedolizumab IV

**Date:** 28 November 2016      **Amendment Number:** 05

**Amendment History:**

Date	Amendment Number	Amendment Type	Region
15 December 2014	Initial Protocol	Not applicable	Global
23 January 2015	01	Substantial	Global
01 September 2015	02	Non-substantial	France
09 December 2015	03	Non-substantial	Italy
28 April 2016	04	Substantial	Global
28 November 2016	05	Substantial	Czech Republic, Hungary, Italy and Poland

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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	<i>Americas:</i> Fax: PPD Email: [REDACTED]
Medical Monitor (medical advice on protocol and compound)	<i>Europe/ROW:</i> PPD
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

## **1.2 Approval**

### **REPRESENTATIVES OF TAKEDA**

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

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

### **SIGNATURES**

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

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

PPD \_\_\_\_\_ Date PPD \_\_\_\_\_ Date



## **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.

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Signature of Investigator

Date

---

Investigator Name (print or type)

---

Investigator's Title

---

Location of Facility (City, State/Provence)

---

Location of Facility (Country)

### **1.3 Protocol Amendment No. 05 Summary of Changes**

#### **Rationale for Amendment No. 05**

This document describes the changes in reference to the Protocol Incorporating Amendment No. 05.

The primary purpose of this amendment is to update the protocol to allow subjects in participating countries to transition into an Extended Access Program (XAP). Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in [Appendix H](#).

#### **Changes in Amendment No. 05**

1. Allow all subjects (who complete Part B) in countries where vedolizumab is either not commercially available or is not reimbursed, continued access to vedolizumab by transition into an Extended Access Program (XAP), Vedolizumab-4013.
2. Remove the requirement for subjects who transition into the XAP study to attend the 18-week Safety Follow-up Visit in the MLN0002-3028 study. The safety of these subjects will be monitored as part of the XAP study.
3. Remove the requirement for subjects who transition into the XAP study to participate in the 6-month long-term follow-up safety questionnaire in the MLN0002-3028 study. The safety of these subjects will be monitored as part of the XAP study.
4. Amend the adverse event, serious adverse event, and concomitant medication reporting instructions for subjects who transition into the XAP study, such that the MLN0002-3028 collection period ends at the time the subject is consented into the XAP.
5. Administrative change to the Responsible Medical Officer.

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## **2.0 STUDY SUMMARY**

<b>Name of Sponsor(s):</b> Takeda Development Center Americas, Inc. Takeda Development Centre Europe, Ltd.	<b>Compound:</b> Vedolizumab IV			
<b>Title of Protocol:</b> An Open-Label Phase 3b Study to Assess Mucosal Healing in Subjects With Moderately to Severely Active Crohn's Disease Treated With Vedolizumab IV	<b>IND No.:</b> 9,125	<b>EudraCT No.:</b> 2014-003509-13		
<b>Study Number:</b> MLN0002-3028	<b>Phase:</b> 3b			
<b>Study Design:</b>  This is a phase 3b single-arm, open-label multicenter study to evaluate the efficacy and safety of vedolizumab 300 mg intravenous (IV) infusion over a 26 week-treatment period using ileocolonoscopy in subjects with moderately to severely active Crohn's Disease (CD) (Part A) followed by a 26 week-treatment extension period (Part B). Approximately 100 subjects who have failed treatment with corticosteroids, immunomodulator, and/or biologics will be enrolled. Subjects who are tumor necrosis factor- alpha (TNF- $\alpha$ ) antagonist naïve as well as those who are TNF- $\alpha$ antagonist failures will be included, such that approximately 50% of enrolled subjects are TNF- $\alpha$ antagonist naïve. A magnetic resonance enterography (MREn) substudy will be conducted at selected centers to assess bowel wall activity.				
<b>Primary Objectives:</b> To evaluate endoscopic remission at Week 26 as assessed by ileocolonoscopy.				
<b>Secondary Objectives:</b>				
<b>Part A</b> <ul style="list-style-type: none"><li>• To examine the relationship among endoscopic, imaging, histological, and clinical assessments of CD.</li><li>• To evaluate endoscopic remission at Week 14.</li><li>• To evaluate endoscopic response at Weeks 14 and 26.</li><li>• To evaluate clinical response assessed by Crohn's Disease Activity Index (CDAI) at Weeks 10 and 26.</li><li>• To evaluate clinical remission assessed by CDAI at Weeks 10 and 26.</li></ul>				
<b>Part B</b> <ul style="list-style-type: none"><li>• To examine the relationship among endoscopic, imaging, histological, and clinical assessments of CD.</li><li>• To evaluate endoscopic remission at Week 52.</li><li>• To evaluate endoscopic response at Week 52.</li><li>• To evaluate clinical response assessed by Crohn's Disease Activity Index (CDAI) at Week 52.</li><li>• To evaluate clinical remission assessed by CDAI at Weeks 52</li><li>• To evaluate durable endoscopic remission at Week 52 in subjects with endoscopic remission at Week 26.</li></ul>				
<b>Subject Population:</b> Adult subjects aged 18-80 years inclusive, with CD				
<b>Number of Subjects:</b> Approximately 100 subjects	<b>Number of Sites:</b> Approximately 75 sites in North America and Europe			
<b>Dose Level(s):</b> Vedolizumab IV 300 mg	<b>Route of Administration:</b> Intravenous			

<b>Duration of Treatment:</b>  Total 52-week treatment period: Part A: 26-week treatment period Part B: 26-week treatment extension period	<b>Period of Evaluation:</b>  The study includes a 4-week screening period, a 52-week treatment period split into 2 parts, and an 18-week follow-up period following last dose. The duration of the study will be approximately 70 weeks. Subjects who do not transition to the Extended Access Program (XAP), Vedolizumab-4013 will participate in a 6-month safety follow-up phone survey after last dose. Subjects who transition into the XAP study are not required to participate in the 18-week follow-up period or the 6-month safety follow-up phone survey. The safety of these subjects will be monitored as part of the XAP study.
<b>Main Criteria for Inclusion:</b>  Subjects who have had a diagnosis of moderately to severely active CD for at least 3 months prior to enrollment, with a CDAI of 220-450 during the screening period, a simple endoscopic score for CD (SES-CD) score of $\geq 7$ <b>and</b> presence of at least one mucosal ulceration documented by recorded ileocolonoscopy at Screening assessed by the central reader.  Subjects who have CD involvement of the ileum and/or colon that can be assessed by ileocolonoscopy. Subjects who have demonstrated an inadequate response to, loss of response to, or intolerance of corticosteroids, immunomodulators and/or TNF- $\alpha$ antagonists.	
<b>Main Criteria for Exclusion:</b>  Subjects who have any evidence of an active infection during Screening. Subjects who have a positive progressive multifocal leukoencephalopathy (PML) subjective checklist during Screening and before the administration of study drug on Day 1. Subjects who have received any biologics within 60 days of enrollment. Subjects who have had prior exposure to vedolizumab, natalizumab, efalizumab, or rituximab.	
<b>Main Criteria for Evaluation and Analyses:</b>  The primary endpoint for this study is the proportion of subjects achieving endoscopic remission, defined as SES-CD score of $\leq 4$ at Week 26.  Secondary endpoints for Part A are: <ul style="list-style-type: none"><li>• Proportion of subjects achieving complete mucosal healing (defined as absence of ulceration) at Week 26.</li><li>• Proportion of subjects achieving endoscopic remission at Week 14.</li><li>• Proportion of subjects with endoscopic response (defined as SES-CD reduction by <math>\geq 50\%</math>) at Week 14.</li><li>• Proportion of subjects with endoscopic response (defined as SES-CD reduction by <math>\geq 50\%</math>) at Week 26.</li><li>• Proportion of subjects achieving clinical response (CDAI decrease from Baseline <math>\geq 100</math> points) at Week 10.</li><li>• Proportion of subjects achieving clinical response (CDAI decrease from Baseline <math>\geq 100</math> points) at Week 26.</li><li>• Proportion of subjects achieving clinical remission (CDAI <math>\leq 150</math> points) at Week 10.</li><li>• Proportion of subjects achieving clinical remission (CDAI <math>\leq 150</math> points) at Week 26.</li></ul> Secondary endpoints for Part B are: <ul style="list-style-type: none"><li>• Proportion of subjects achieving complete mucosal healing (defined as absence of ulceration) at Week 52.</li><li>• Proportion of subjects achieving endoscopic remission at Week 52.</li><li>• Proportion of subjects with endoscopic response (defined as SES-CD reduction by <math>\geq 50\%</math>) at Week 52.</li><li>• Proportion of subjects achieving clinical response (CDAI decrease from Baseline <math>\geq 100</math> points) at Week 52.</li><li>• Proportion of subjects achieving clinical remission (CDAI <math>\leq 150</math> points) at Week 52.</li><li>• Proportion of subjects with durable clinical remission, defined as clinical remission at Week 26 and Week 52.</li></ul>	

**Statistical Considerations:**

All proportion-based efficacy endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

All change from baseline efficacy endpoints will be summarized descriptively by time point.

Three interim analyses will be conducted for final efficacy at Weeks 14, 26, and 52, and for safety.

**Sample Size Justification:**

A sample size of 100 subjects will be sufficient to provide a 95% confidence interval based on normal approximation for the primary endpoint (endoscopic remission rate at Week 26) that extends no more than 10% in each direction from the estimated rate.

### **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 for specific study-related activities will perform these activities in full or in partnership with the sponsor.

#### **3.2 Principal Investigator/Coordinating Investigator**

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

### **3.3 List of Abbreviations**

5-ASA	5-aminosalicylate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
AVA	anti-vedolizumab antibody; also called HAHA
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate (renal system)
EMA	European Medicines Agency
EQ-5D	Euro Quality of Life-5D
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
GI	gastrointestinal(ly)
HAHA	human antihuman antibody
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
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
ICD	implantable cardioverter defibrillators
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
Ig	immunoglobulin
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)

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IVRS	interactive voice response system
IWRS	interactive web response system
LTFU	long-term follow-up
LFT	liver function test
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MarIA	Magnetic Resonance Index of Activity
MedDRA	Medical Dictionary for Regulatory Activities
MR	magnetic resonance
MREn	magnetic resonance enterography
PD	pharmacodynamic(s)
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
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
SES-CD	simple endoscopic score for Crohn's Disease
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TPMT	thiopurine S-methyltransferase
TNF- $\alpha$	tumor necrosis factor- alpha
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
XAP	Extended Access Program

### **3.4 Corporate Identification**

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

## **4.0 INTRODUCTION**

### **4.1 Background**

#### **4.1.1 Diseases 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).

CD is manifested by asymmetric, and transmural inflammation of the digestive tract. In contrast to the diffuse, superficial, continuous inflammation limited to the colon in UC, the inflammation of CD is focal, may be transmural, and can involve any segment of the GI tract from mouth to anus. The prevalence of CD is approximately 150/100,000 of the US population and approximately 125/100,000 of population in Western Europe [2-4]. The characteristic pathology involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration.

Clinical manifestations of CD include diarrhea, 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 CD 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 IBD but have numerous limitations for patients with moderately to severely active disease. Mild to moderately active CD has commonly been treated with oral 5-aminosalicylates (5-ASAs); despite their use in the past, the benefit is debatable [5,6]. Corticosteroids are often required for the one-third of patients who fail to respond to 5-ASAs. While highly effective for induction of remission, corticosteroids are not recommended for the maintenance of remission in CD because they 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 of moderately to severely active CD. 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 [7]. Other severe adverse events include cytopenias, hepatitis, and infection. Methotrexate, while ineffective in UC, has a role in the management of refractory CD; however, it also demonstrates a number of dose-limiting toxicities. Antibiotics have marginal efficacy in maintenance of remission in CD.

Monoclonal antibodies (mAbs) directed against tumor necrosis factor alpha (TNF- $\alpha$ ) have been approved for treatment of UC and CD in the United States and European Union, including infliximab (Remicade), administered by IV infusion, and adalimumab (Humira) or certolizumab (Cimzia) administered by subcutaneous (SC) injection [8-10]. These agents have substantially improved the care of patients with CD by inducing and maintaining remission and decreasing the

need for hospitalization, surgeries, and other complications. Although TNF- $\alpha$  antagonists represent an important addition to the pharmacologic armamentarium for CD, they are effective in only a subset of patients, with roughly two-thirds of patients in controlled trials not in remission at the end of the first year of therapy [11,12]. In addition, controlled studies have demonstrated that, after failure of 1 TNF- $\alpha$  antagonist, a patient's response to a second TNF- $\alpha$  antagonist is substantially lower [13]. The TNF- $\alpha$  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 [8,9].

Although not authorized in the European Union, another biological therapy, natalizumab (TYSABRI<sup>®</sup>), has been approved in the United States for induction and maintenance of remission in patients with moderately to severely active CD. Natalizumab blocks the  $\alpha$ 4 integrin, a cell surface marker on peripheral circulating lymphocytes and thereby inhibits both  $\alpha$ 4 $\beta$ 1 and  $\alpha$ 4 $\beta$ 7 integrins. However, due to the increased risk of developing the rare but often fatal neurodegenerative disorder, progressive multifocal leukoencephalopathy (PML), which is a mechanism-based side effect, natalizumab is cautiously prescribed for treatment of CD [14].

Surgical removal of highly diseased, strictured, or stenotic segments of bowel in CD is not curative. Relapse occurs in a majority of patients with CD who undergo segmental resections, and the need for additional surgery is the rule rather than the exception [15]. The limitations of current therapies for IBD 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 [16-19]. 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 [20]. Vedolizumab has been developed as a treatment for ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by inflammation of the gastrointestinal (GI) tract.

Vedolizumab IV (Entyvio<sup>TM</sup>) is a lyophilized powder which after appropriate reconstitution and dilution is intended for intravenous (IV) infusion that has been granted marketing approval in several regions, including the United States (US), European Union (EU), and Australia. Vedolizumab IV is approved for the treatment of adult patients with moderately to severely active UC or CD who have failed conventional treatment, (eg, immunomodulators, corticosteroids, or tumor necrosis factor-alpha (TNF- $\alpha$ ) antagonists). The 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 [20].

#### *4.1.2.2 Human Experience*

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 [21-23]. As of 20 July 2014, vedolizumab exposure has extended for  $\geq 12$  months in 1667 subjects,  $\geq 24$  months in 1119 subjects,  $\geq 36$  months in 793 subjects, and  $\geq 48$  months in 374 subjects.

In subjects with moderately to severely active CD (Study C13007), including subjects who had failed treatment with 1 or more therapies including TNF- $\alpha$  antagonists, vedolizumab 300 mg infusion at Week 0 and Week 2 (induction) followed by either Q4W or Q8W from Week 6 through Week 52 (maintenance) demonstrated statistically significant differences in efficacy compared to placebo for both the induction phase and maintenance phase. The study met its primary endpoint for the induction phase, clinical remission at Week 6 but did not meet the second primary endpoint of enhanced clinical response (CDAI-100) at Week 6 in the overall population although the treatment difference favored vedolizumab. The study did meet its primary endpoint for the maintenance phase, clinical remission at Week 52, as well as important secondary endpoints, including enhanced clinical response at Week 52 and corticosteroid-free clinical remission at Week 52 [22].

In Study C13011, vedolizumab (300 mg infusion at Weeks 0, 2, and 6) was administered to subjects with moderately or severely active CD who had failed conventional therapies, including TNF- $\alpha$  antagonists. The primary endpoint of clinical remission at Week 6 in the TNF- $\alpha$  antagonist failure intent-to-treat (ITT) population was not met; however, a treatment difference was observed at Week 10 in this population. Similar treatment differences favoring vedolizumab were also demonstrated for the overall population and in the subgroup of subjects who were TNF- $\alpha$  antagonist naïve [23].

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. 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).

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 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 C13008 is consistent with safety in the completed studies.

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 was well tolerated in clinical studies.

#### **4.2 Rationale for the Proposed Study**

The current study is designed to further explore the effects of vedolizumab on mucosal healing as assessed by traditional colonoscopy, histology, and transmural bowel wall activity, via a substudy using magnetic resonance enterography (MREn).

Colonoscopy is used to evaluate CD disease extension and activity. Endoscopy has some drawbacks, including invasiveness, procedure discomfort, risk of bowel perforation, and relatively poor patient acceptance. The goals of imaging in CD include determination of anatomical location

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and severity of disease, identification of complications such as fibrostenotics or penetrating disease, assessment of response to therapy, and identification of extraintestinal complication of the disease [28]. Because CD is thought to be a transmural disease, cross sectional imaging techniques such as magnetic resonance (MR) enterography and CT enterography are superior to ileocolonoscopy in their ability to assess the full thickness of the intestinal wall and disease processes extending deeper than the mucosa [29]. The search for techniques that allow disease extension and inflammation assessment with a minimally invasive approach has led to the study of MR in CD. MR enterography (MREn) is characterized by multi-parametric excellent soft tissue characterization and lack of ionizing radiation. The MREn activity index has been cited by authors and endorsed by European Crohn's and Colitis Organisation as beneficial for assessment of healing of inflammatory lesions [1].

Histological evidence of mucosal healing has been shown with sustained reduction in the expression of inflammatory markers [11]. The present study will examine histology markers of inflammation related to mucosal disease.

The current goals of CD treatment include: steroid-free sustained clinical remission; induction and maintenance of endoscopic mucosal healing; potential induction and maintenance of radiological healing; prevention of surgery; maintenance of normal GI function; and prevention of disability. To achieve these goals, the therapeutic regimen should be able to treat the underlying inflammation and heal the bowel.

Pharmacogenomic analysis may be conducted to evaluate 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 and disease, which may lead to additional hypothesis-generating exploratory research on stored samples.

#### **4.3 Risk:Benefit Assessment**

The proposed Study MLN0002-3028 is designed to evaluate the efficacy and safety of vedolizumab IV in subjects with moderately to severely active CD. The dosing and administration regimen and study population in Study MLN0002-3028 are consistent with the approved vedolizumab IV label. Overall, vedolizumab has been well tolerated in clinical studies. The procedures performed during the study are part of usual clinical practice. Taking into account the risks associated with procedures and the disease worsening in this population, the benefit-risk profile remains positive for vedolizumab in this study.

## **5.0 STUDY OBJECTIVES AND ENDPOINTS**

### **5.1 Objectives**

#### **5.1.1 Primary Objective**

To evaluate endoscopic remission at Week 26 as assessed by ileocolonoscopy.

#### **5.1.2 Secondary Objectives**

Part A

- To examine the relationship among endoscopic, imaging, histological, and clinical assessments of CD.
- To evaluate endoscopic remission at Week 14.
- To evaluate endoscopic response at Weeks 14 and 26.
- To evaluate clinical response assessed by Crohn's Disease Activity Index (CDAI) at Weeks 10 and 26.
- To evaluate clinical remission assessed by CDAI at Weeks 10 and 26.

Part B

- To examine the relationship among endoscopic, imaging, histological, and clinical assessments of CD.
- To evaluate endoscopic remission at Week 52.
- To evaluate endoscopic response at Week 52.
- To evaluate clinical response assessed by CDAI at Week 52.
- To evaluate clinical remission assessed by CDAI at Week 52.
- To evaluate durable endoscopic remission at Week 52 in patients with endoscopic remission at Week 26.

#### **5.1.3 Additional Objectives**

Part A

- To evaluate changes in transmural bowel wall activity and other measures of bowel wall inflammation using MREn at Week 26.
- To assess histological response at Week 26.
- To evaluate C-reactive protein (CRP) at Weeks 10 and 26.
- To evaluate fecal calprotectin at Weeks 14 and 26.

- To evaluate immunogenicity of vedolizumab.
- To evaluate health-related quality of life (as assessed by inflammatory bowel disease questionnaire [IBDQ] and Euro Quality of Life-5D [EQ-5D]) at Weeks 14 and 26.
- To explore the relationship between endoscopic remission and health-related quality of life (QOL).
- To evaluate impact on loss of work productivity and activity impairment assessed by Work Productivity and Activity Impairment (WPAI):CD at Weeks 14 and 26.

#### **Part B**

- To evaluate changes in transmural bowel wall activity and other measures of bowel wall inflammation using MREn at Week 52.
- To assess histological response at Week 52.
- To evaluate CRP at Weeks 38 and 52.
- To evaluate fecal calprotectin at Weeks 38 and 52.
- To evaluate immunogenicity of vedolizumab.
- To evaluate clinical response assessed by CDAI at Weeks 38 and 46.
- To evaluate clinical remission assessed by CDAI at Weeks 38 and 46.
- To evaluate health-related quality of life (IBDQ and EQ-5D) at Weeks 38 and 52.
- To explore the relationship between endoscopic remission and health-related QOL.
- To evaluate impact on loss of work productivity and activity impairment assessed by WPAI:CD at Week 52.

### **5.2 Endpoints**

#### **5.2.1 Primary Endpoints**

The primary endpoint is the proportion of subjects achieving endoscopic remission, defined as a simple endoscopic score for Crohn's Disease (SES-CD) score of  $\leq 4$  at Week 26.

#### **5.2.2 Secondary Endpoints**

The secondary endpoints for Part A are:

- Proportion of subjects achieving complete mucosal healing (defined as absence of ulceration) at Week 26.
- Proportion of subjects achieving endoscopic remission at Week 14.

- Proportion of subjects with endoscopic response (defined as SES-CD reduction by  $\geq 50\%$ ) at Week 14.
- Proportion of subjects with endoscopic response (defined as SES-CD reduction by  $\geq 50\%$ ) at Week 26.
- Proportion of subjects achieving clinical response (CDAI decrease from Baseline of  $\geq 100$  points) at Week 10.
- Proportion of subjects achieving clinical response (CDAI decrease from Baseline of  $\geq 100$  points) at Week 26.
- Proportion of subjects achieving clinical remission (CDAI  $\leq 150$ ) at Week 10.
- Proportion of subjects achieving clinical remission (CDAI  $\leq 150$ ) at Week 26.

The secondary endpoints for Part B are:

- Proportion of subjects achieving complete mucosal healing (defined as absence of ulceration) at Week 52.
- Proportion of subjects achieving endoscopic remission at Week 52.
- Proportion of subjects with endoscopic response (defined as SES-CD reduction by  $\geq 50\%$ ) at Week 52.
- Proportion of subjects achieving clinical response (CDAI decrease from Baseline of  $\geq 100$  points) at Week 52.
- Proportion of subjects achieving clinical remission (CDAI  $\leq 150$ ) at Week 52.
- Proportion of subjects with durable clinical remission, defined as clinical remission at Week 26 and Week 52.

### **5.2.3 Additional Endpoints**

The additional endpoints for Part A are:

- Change from Baseline to Week 26 in individual MREn parameters (including wall thickening, relative contrast enhancement, presence of ulcerations, presence of edema) for each ileocolonic segment and for more proximal bowel segments, if evaluable.
- Proportion of subjects achieving Magnetic Resonance Index of Activity (MaRIA) score  $< 7$  at Week 26 globally and on a per segment basis.
- Proportion of subjects with 25% and 75% reduction of SES-CD at Weeks 14 and 26.
- Proportion of subjects with no granulocytes present in bowel biopsy at Week 26.
- Proportion of subjects with a change in histology at Week 26.

- Proportion of subjects with elevated CRP at Baseline who achieve normalization of CRP at Weeks 10 and 26.
- Change from Baseline to Weeks 14 and 26 in fecal calprotectin.
- Proportion of subjects positive for anti-vedolizumab antibody (AVA; also called human antihuman antibody [HAHA]) at Baseline, Week 26, and at the Postdose 18-week Safety Follow-up Visit.
- Proportion of subjects with positive neutralizing AVA at Baseline, Week 26, and at the Postdose 18-week Safety Follow-up Visit.
- Change from Baseline to Weeks 14 and 26 in the IBDQ total and subscale scores.
- Change from Baseline to Weeks 14 and 26 in the EQ-5D utility score and visual analog scale (VAS) score.
- Change from Baseline to Weeks 14 and 26 in percent work time missed due to CD.
- Change from Baseline to Weeks 14 and 26 in percent impairment while working due to CD.
- Change from Baseline to Weeks 14 and 26 in percent overall work impairment due to CD.
- Change from Baseline to Weeks 14 and 26 in percent activity impairment due to CD.
- AEs, SAEs, vital signs, and laboratory tests.

The additional endpoints for Part B are:

- Change from Baseline to Week 52 in individual MREn parameters (including wall thickening, relative contrast enhancement, presence of ulcerations, presence of edema) for each ileocolonic segment and for more proximal bowel segments, if evaluable.
- Proportion of subjects achieving MaRIA score  $<7$  at Week 52 globally and on a per segment basis.
- Proportion of subjects with 25% and 75% reduction of SES-CD at Week 52.
- Proportion of subjects with no granulocytes present in bowel biopsy at Week 52.
- Proportion of subjects with a change in histology at Week 52.
- Proportion of subjects with elevated CRP at Baseline who achieve normalization of CRP at Weeks 38 and 52.
- Change from Baseline to Weeks 38 and 52 in fecal calprotectin.
- Proportion of subjects positive for AVA at Week 52 and at the Postdose 18-week Safety Follow-up Visit (for subjects not transitioning into the Extended Access Program [XAP] study).

- Proportion of subjects with positive neutralizing AVA at Week 52, at the Postdose 18-week Safety Follow-up Visit (for subjects not transitioning into the XAP study).
- Proportion of subjects achieving clinical response (CDAI decrease from Baseline of  $\geq 100$  points) at Weeks 38 and 46.
- Proportion of subjects achieving clinical remission (CDAI  $\leq 150$ ) at Week 38 and 46.
- Change from Baseline to Weeks 38 and 52 in the IBDQ total and subscale scores.
- Change from Baseline to Weeks 38 and 52 in the EQ-5D utility score and VAS score.
- Change from Baseline to Week 52 in percent work time missed due to CD.
- Change from Baseline to Week 52 in percent impairment while working due to CD.
- Change from Baseline to Week 52 in percent overall work impairment due to CD.
- Change from Baseline to Week 52 in percent activity impairment due to CD.
- AEs, SAEs, vital signs, and laboratory tests.

## **6.0 STUDY DESIGN AND DESCRIPTION**

### **6.1 Study Design**

This is a phase 3b single-arm, open-label multicenter study to evaluate the efficacy and safety of vedolizumab 300 mg IV infusion over a 26-week treatment period using ileocolonoscopy for the assessment in subjects with moderately to severely active CD (Part A) followed by a 26 week-treatment extension period (Part B). Biopsies will be collected for histological assessments per the schedule of events for all subjects. The study will be conducted at sites in North America and Europe. The 26-week treatment extension (Part B) is included as part of Protocol Amendment No. 04 (dated 27 April 2016), ongoing subjects at the time of the amendment will have the option to either stop treatment at Week 26 (Part A) or continue treatment into Part B. Subjects who enrol into the study after Protocol Amendment No. 04 will be treated directly for 52 weeks (Part A and B).

Approximately 100 subjects with moderately to severely active CD who have failed treatment with corticosteroids, immunosuppressants, and/or biologics will be enrolled. Subjects who are TNF- $\alpha$  antagonist naïve as well as those who are TNF- $\alpha$  antagonist failures will be included, such that approximately 50% of enrolled subjects are TNF- $\alpha$  antagonist naïve.

The study consists of a 4-week screening period, a 26-week treatment period (Part A), followed by a 26-week extension treatment period (Part B from Week 30 to 52 with last dose at Week 46), and an 18-week follow-up period following the last dose. The duration of the study will be approximately 44 weeks for subjects completing Part A, and 70 weeks for subjects completing Part B. All subjects included in the study will also have a 6-month safety follow-up telephone call following the last dose. End of trial will be the date of the last visit of the last subject at the Postdose 18-week Safety Follow-up visit. The Postdose 18-week Safety Follow-up visit is described in Section 9.3.4.

Subjects who consent to Part B will have the option to voluntarily enroll into an XAP study after the Final Visit or Week 52 of MLN0002-3028. Subjects who transition into the XAP study will not take part in the 18-week follow-up period or the 6-month safety follow-up telephone call following their last dose in MLN0002-3028. The end of trial will be the Week 52 visit for these subjects and the duration of the study will be approximately 56 weeks.

Subjects that meet all the inclusion criteria and none of the exclusion criteria will be dosed on site with vedolizumab 300 mg IV. Subjects will visit the site for dosing at Day 1, Weeks 2, 6, 14, and 22 for Part A, and at Weeks 30, 38, and 46 for Part B. Ileocolonoscopy will be performed at the Screening, Weeks 14, 26 (Part A), and 52 (Part B) or early termination (ET) visits. Biopsies will be taken during the Screening, Weeks 26 (Part A), and 52 (Part B) or ET visit. All ileocolonoscopies will be evaluated by a central reader.

An MREn substudy will be conducted at selected qualified centers using a standardized MR acquisition and procedure to assess bowel wall activity. Only subjects from the pre-selected sites will be included in this study; these subjects will undergo an MREn assessment at the Screening,

Weeks 26 (Part A), and 52 (Part B) or ET visit, unless they have contraindications to the procedure. All MREn results will be evaluated by an independent central reader.

**Figure 6.a Schematic of Study Design: For Subjects on 26 Weeks of Treatment**

<b>Days -28 to -1</b>	<b>Day 1</b>	<b>Part A Weeks 2, 6, 10, 14, 22, 26</b>	<b>Week 26</b>	Postdose 18-week Safety Follow-up Visit	6-month Telephone Follow-up
Screening	1st dose 300 mg IV	300 mg IV (all visits except Week 10 and 26)	Final Visit / Early Termination Visit		

**Figure 6.b Schematic of Study Design: For Subjects on 52 Weeks of Treatment**

<b>Days -28 to -1</b>	<b>Day 1</b>	<b>Part A Weeks 2, 6, 10, 14, 22, 26</b>	<b>Part B Weeks 30, 38, 46</b>	<b>Week 52</b>	Postdose 18-week Safety Follow-up Visit (a)	6-month Telephone Follow-up (a)
Screening	1st dose 300 mg IV	300 mg IV (all visits except Week 10 and 26)	300 mg IV	Final Visit / Early Termination Visit		

(a) Not applicable for subjects who transition into the XAP study.

## **6.2 Justification for Study Design, Dose, and Endpoints**

CD is a chronic inflammatory disorder of the GI tract. CD can impact any part of the digestive tract and symptoms commonly include abdominal pain, diarrhea, rectal bleeding, weight loss, and fever. The exact cause remains unknown. The aim of current CD treatments is to induce and maintain remission, or achieve extended periods of remission.

Treatment options include corticosteroids, antimetabolites (6-mercaptopurine, azathioprine, or methotrexate), and TNF- $\alpha$  antagonists. In 2013, results from the phase 3, randomized controlled C13007 trial demonstrated the efficacy of vedolizumab in inducing remission at Week 6 in adult subjects with moderately to severely active CD [22]. Results from the maintenance study C13007 showed that vedolizumab maintained remission in the broad population with CD and in those who had failed treatment with TNF- $\alpha$  antagonists.

The objective of this study is to assess endoscopic remission at Week 26 after treatment with open label vedolizumab using ileocolonoscopy and histology as well as an assessment of CD activity in the bowel wall in a substudy using MREn. The study has been extended to 52 weeks to gather long-term mucosal healing data with vedolizumab. The study has the potential to guide the understanding of mucosal healing in CD subjects and the effect of vedolizumab. Subjects that meet the eligibility criteria will receive open-label vedolizumab 300 mg IV.

## **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 objective 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 first dose.

### 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 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 moderately to severely active CD at least 3 months prior to enrollment, with a CDAI score of 220-450 during the Screening Period, a SES-CD score of  $\geq 7$  **and** presence of at least one mucosal ulceration documented by recorded ileocolonoscopy at Screening assessed by the central reader.
4. The subject has CD with involvement of the ileum and/or colon that can be assessed by ileocolonoscopy.
5. The subject is male or female and aged 18 to 80 years, inclusive.
6. 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.
7. 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 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

8. The subject has demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:

- Immunomodulators:
  - i. The subject has signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of oral azathioprine ( $\geq 1.5$  mg/kg) or 6-mercaptopurine ( $\geq 0.75$  mg/kg), OR
  - ii. The subject has a history of intolerance (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, thiopurine S-methyltransferase non wild type [where wild type is defined as TPMT\*1/\*1], infection) to at least 1 immunomodulator.

- TNF- $\alpha$  antagonists:
  - i. The subject has signs and symptoms of persistently active disease despite a history of at least 1 induction with:
    - a) Infliximab: 4-week regimen of 5 mg/kg, 2 doses at 2 weeks apart, OR
    - b) Adalimumab: 2-week regimen of 160 mg on Day 1 and 80 mg on Day 15, OR
    - c) Certolizumab: 4-week regimen of 400 mg initially at Weeks 0, 2, 4 OR
  - ii. The subject has recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), OR
  - iii. The subject has a history of intolerance of infliximab, adalimumab, or certolizumab, including but not limited to, infusion-related reaction, demyelination, congestive heart failure, or infection.
- Corticosteroids
  - i. Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or IV for 1 week, OR
  - ii. Signs and symptoms of persistently active disease despite treatment with budesonide 9 mg daily or 6 mg daily for maintenance, OR
  - iii. At least one failed attempt to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally, OR
  - iv. History of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection).
- 9. The subject may be receiving a stable therapeutic dose of conventional therapies for CD as defined by protocol Section 7.3.1 (excluding other biologic agents 60 days before enrollment).
- 10. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factors must be up-to-date on colorectal cancer surveillance (may be performed during Screening).

## **7.2 Exclusion Criteria**

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received a diagnosis of ulcerative colitis or indeterminate colitis.
2. The subject has clinical evidence of abdominal abscess.
3. The subject has a history of >3 small bowel resections or diagnosis of short bowel syndrome.
4. The subject has extensive colonic resection, ie, subtotal or total colectomy with <15 cm colon remaining.

5. The subject has ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
6. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
7. The subject has a history or evidence of colonic mucosal dysplasia.
8. The subject has intolerance or contraindication to undergo ileocolonoscopy.
9. The subject has active or latent tuberculosis, regardless of treatment history, as evidenced by any of the following:
  - a) History of TB.
  - b) A diagnostic TB test performed during screening that is positive, as defined by:
    - i. A positive QuantifERON® test or 2 successive indeterminate QuantifERON tests **OR**
    - ii. A tuberculin skin test reaction  $\geq 10$  mm ( $\geq 5$  mm in patients receiving the equivalent of  $> 15$  mg/day prednisone).
10. The subject has chronic hepatitis B (HBV) or hepatitis C (HCV) infection.
11. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
12. The subject has evidence of active *C. difficile* infection or is having treatment for *C. difficile* infection or other intestinal pathogens during Screening.
13. The subject has evidence of an active infection during Screening.
14. The subject currently requires or has a planned surgical intervention for CD during the study.
15. The subject has received any investigational compound within 60 days of enrollment.
16. The subject has received any biologics within 60 days of enrollment.
17. The subject has received any live vaccinations within 30 days prior to enrollment.
18. The subject has conditions which, in the opinion of the investigator, may interfere with the subject's ability to comply with the study procedures.
19. 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.
20. The subject has a history of hypersensitivity or allergies to vedolizumab or its components.
21. The subject has had prior exposure to vedolizumab, natalizumab, efalizumab, or rituximab.
22. The subject had a surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.

23. The subject has a history of malignancy, except for the following: adequately-treated nonmetastatic basal cell skin cancer; squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to Screening; and history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to screening. Subjects with a 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 enrollment.
24. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
25. The subject has a positive PML subjective symptom checklist during Screening or prior to the administration of study drug on Day 1.
26. The subject has any of the following laboratory abnormalities during the Screening Period:
  - i. Hemoglobin level <8 g/dL.
  - ii. White blood cell (WBC) count <3 x 10<sup>9</sup>/L.
  - iii. Lymphocyte count <0.5 x 10<sup>9</sup>/L.
  - iv. Platelet count <100 x 10<sup>9</sup>/L or >1200 x 10<sup>9</sup>/L.
  - v. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x the upper limit of normal (ULN).
  - vi. Alkaline phosphatase >3 x ULN.
  - vii. Serum creatinine >2 x ULN.
27. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to enrollment.
28. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
29. The subject is unable to attend all the study visits or comply with study procedures.
30. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
31. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
32. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

33. Subjects who are at sites participating in the MREn substudy may not participate if they have intolerance or contraindication to the procedure or if any of the following exclusions apply:

- a) The subject has certain implanted medical devices, such as pacemakers or implantable cardioverter defibrillators (ICDs), or ferromagnetic metallic foreign bodies, such as shrapnel or certain tattoos.
- b) The subject has allergy to gadolinium-based MR IV contrast agents.
- c) The subject has known claustrophobia.
- d) The subject has estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m<sup>2</sup> at Screening.

### **7.3 Excluded Medications and Treatments**

The following medications are excluded from use during the study:

- Any treatment for CD other than those listed in Section 7.3.1 (either approved or investigational).
- All live vaccines during the study treatment period 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, other than localized injections (eg, intra-ocular injections for wet macular degeneration).

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 and Treatments**

The following medications are permitted during the study:

- Immunomodulators (methotrexate, azathioprine, 6-mercaptopurine), stable for at least 8 weeks prior to enrollment.
- Oral 5-ASAs, probiotics, or antibiotics for CD, stable for at least 2 weeks prior to enrollment.
- Anti-diarrheals for control of chronic diarrhea.

##### *7.3.1.1 Oral Corticosteroid Dosing and Tapering*

The maximum dose of oral corticosteroids for the treatment of CD that may be co-administered with vedolizumab as a long-term regimen is 30 mg/day prednisone or 9 mg/day budesonide with 6 mg/day for maintenance (or equivalent) as long as they have been stable for at least 4 weeks prior to enrollment or for 2 weeks prior to enrollment if being tapered. Short-term use of higher doses is acceptable; however, patients who require consistent higher doses should be withdrawn from the study.

It is strongly recommended that patients receiving oral corticosteroids should begin a tapering regimen once they either achieve clinical response or if, in the opinion of the Investigator, they have demonstrated sufficient improvement. The recommended tapering schedule is as follows:

- For prednisone at doses  $>10$  mg/day (or equivalent), the dose should be reduced at a rate of 5 mg/week until a 10 mg/day is reached.
- For prednisone at doses  $\leq 10$  mg/day (or equivalent) or once a 10 mg/day dose (or equivalent) is achieved by tapering, the dose should be reduced at a rate of 2.5 mg/week until discontinuation.
- Budesonide should be reduced at a rate of 3 mg every 3 weeks.

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence, such premedication is 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.

#### **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 electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section [9.1.20](#).

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
  - Liver Function Test (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  $>8 \times$  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. Significant protocol deviation. The discovery after the first dose of study medication that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

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

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section [9.1.11](#).

7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Other. 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 the investigator. In addition, efforts should be made to perform all procedures scheduled for the ET 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**

##### *8.1.1.1 Vedolizumab IV*

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.

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.

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.

#### **8.1.2 Storage**

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

Vedolizumab IV must be stored at 2°C to 8°C (36°F to 46°F). A daily temperature log of the drug storage area must be maintained every working day.

#### **8.1.3 Dose and Regimen**

The dose and dosing regimen for all subjects is provided in [Table 8.a](#).

**Table 8.a Dose and Regimen**

<b>Treatment Group</b>	<b>Dose</b>	<b>Treatment Description</b>	
All Subjects	Vedolizumab IV 300 mg	Open-label	Part A: Day 1, Weeks 2, 6, 14, 22 Part B: Weeks 30, 38, 46

#### **8.1.4 Overdose**

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

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

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

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

### **8.2 Investigational Drug Assignment and Dispensing Procedures**

Subjects will receive treatment according to the 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 enroll the subject into the study. The medication identification (ID) number of the investigational drug to be dispensed will then be provided by the IVRS/IWRS as well as at subsequent visits. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IVRS/IWRS. Refer to the study manual provided separately for additional information.

### **8.3 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 (vedolizumab IV 300 mg), 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. 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 with the medication identification 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 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, date and amount dispensed including initials, seal, or signature of the person dispensing the drug.

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

## **9.0 STUDY PLAN**

### **9.1 Study Procedures**

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

#### **9.1.1 Informed Consent Procedure**

The requirements of the informed consent are described in Section [15.2](#).

Informed consent must be obtained 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 of screening; 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 any sample which may be used for pharmacogenomic analysis must be obtained prior to collecting 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 stopped at or within 30 days prior to signing of informed consent.

In addition, all prior biologic medication history for the treatment of Crohn's 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.

#### **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).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw. On dosing days, vitals are taken predose.

#### **9.1.6 Efficacy Measurements**

Efficacy assessments will include ileocolonoscopy with biopsies (when applicable per the schedule of events) to evaluate endoscopic remission and histological response. MREn will be used to evaluate bowel wall activity for a subgroup of subjects. Only confirmed eligible subjects from the pre-selected sites will be included in the MREn substudy.

All efficacy assessments will be reviewed by independent central review. Additional information regarding the central reader assessments and collection and preparation of ileocolonoscopy tissue samples can be found in the Study Manual.

Ileocolonoscopy tissue samples will be collected and stored for future analysis.

##### ***9.1.6.1 Magnetic Resonance Enterography Substudy***

The MREn will be conducted at selected sites qualified to perform MREn as assessed by the imaging core lab designated by the sponsor. A standardized MREn acquisition protocol will be implemented across sites and detailed in an Imaging Manual. eGFR to be assessed prior to MREn being performed. MREn will be performed prior to ileocolonoscopy. De-identified MREn images will be transmitted to the imaging core lab where they will be independently analyzed by expert reviewers. Variables evaluated may include, but are not limited to, wall thickness, enhancement of bowel wall after contrast, mural edema, ulcerations, and perienteric vascularity. Bowel assessments will be made in a segmental manner to allow for direct comparison with ileocolonoscopy assessments (terminal ileum plus ascending, transverse, descending and sigmoid colon, and rectum). More proximal small bowel may also be assessed for abnormalities on MREn only. Several MREn-based activity indices have been proposed and are undergoing validation [28,29]. One or more of these (including MaRIA) will be used to assess therapeutic response and will be compared to endoscopic response (SES-CD) and clinical response (CDAI) scores.

### **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 to the final study visit), 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 or baseline 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 at the time points specified in the schedule of events. The maximum volume of blood at any single visit is approximately 35 mL, and the approximate total volume of blood for the study is 141 mL (94 mL for Part A and 47 mL for Part B). Details of these procedures and required safety monitoring will be given in the laboratory manual.

**Table 9.a Clinical Laboratory Tests**

<b>Hematology</b>	<b>Serum Chemistry</b>	<b>Urinalysis (dipstick)</b>
RBC	ALT	Bilirubin
WBC w/ differential	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	Amylase	Ketones
Platelets	Lipase	Leukocyte esterase
PT/INR	AST	Nitrite
	Total and direct bilirubin	pH
	Total protein	Protein
	Creatinine	Specific Gravity
	Blood urea nitrogen	
	Creatine kinase	
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Bicarbonate	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	
	eGFR (for MREn subjects only)	

**Other:**

HIV	Beta hCG and Urine Pregnancy hCG
Hepatitis panel, including HBsAg and anti-HCV	(female subjects of childbearing potential)
CRP	FSH, if menopause is suspected
AVA	
Pharmacogenomic sample	
Quantiferon for TB	

**Stool:**

Fecal calprotectin
--------------------

FSH=follicle-stimulating hormone, GGT=  $\gamma$ -Glutamyl transferase, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells.

A central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis as well as specialty testing outlined above. The results of safety laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST  $>3 \times$ ULN, follow-up laboratory tests should be performed by the central laboratory 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  $>3 \times$ ULN in conjunction with total bilirubin  $>2 \times$ 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).

#### **9.1.10 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  $>40 \text{ IU/L}$  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:

##### **Intrauterine devices (IUDs):**

- Copper T PLUS condom or spermicide.
- #Progesterone T PLUS condom or spermicide.

##### **#Hormonal contraceptives:**

- Implants.
- Hormone shot/injection.
- Combined pill.
- Minipill.
- Patch.
- Vaginal ring PLUS male condom and spermicide.

Barrier methods (eg, 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) can be used each time the subject has intercourse in addition to methods listed in the table above to ensure acceptable protection level.

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 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 hCG pregnancy test at Screening, subjects also must have a negative hCG pregnancy test prior to receiving any dose of study medication.

### **9.1.11 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 (for subjects not transitioning into the XAP study), should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of study medication or within 18 weeks of the last dose of study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section [1.0](#).

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

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

### **9.1.12 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.

### **9.1.13 Immunogenicity Sample Collection**

Blood specimens for the assessment of AVA will be collected as shown in the schedule of events. A sample will be assessed for neutralizing AVA if a positive AVA is detected.

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

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

#### **9.1.14 Pharmacogenomic Sample Collection**

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

Two whole blood samples (3 mL per sample) for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day 1 from each subject in the study, into plastic K<sub>2</sub> ethylenediamine-tetraacetic acid (EDTA) spray-coated tubes, and stored under frozen conditions. Two whole blood RNA samples (2.5 mL per sample) for RNA pharmacogenomic analysis will be collected on Day 1 from each subject in the study, into a PaxGene™ tube. If DNA or RNA samples are not obtained on Day 1, they may be collected at any point in the study.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets. RNA has multiple vital roles in the codes, decoding, regulation, expression of genes and sensing and communicating responses to cellular signals. Both DNA and RNA from tissues such as blood may be evaluated for the genetic contribution of how the drug is broken down, or how the drug affects the body. This is called a “Pharmacogenomics research study.” Specific purposes of this study include:

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

This information may be used, for example, to develop a better understanding of the safety and efficacy of vedolizumab and other study 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 [Appendix G](#).

### **9.1.15 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](#).

### **9.1.16 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 dosing) 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) Algorithm referenced in Section [11.1.1](#). 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.

### **9.1.17 Crohn's Disease Activity Index**

A CDAI score will be evaluated during screening to determine eligibility, using subject diary entries within 14 days prior to enrollment, and hematocrit results collected during Screening. A CDAI score will also be derived at the time points specified in the Schedule of Events and at any unscheduled visit(s) due to disease exacerbation. See [Appendix E](#).

### **9.1.18 Diary Completion and Review**

Diary entries will be made daily by subjects and will be used for CDAI score calculation. During screening, subjects will be instructed on how to appropriately complete the daily diary. The symptoms of CD must be recorded throughout the study, including the screening period. Diary entries will be made daily by the subject through an electronic system. Entries should be reviewed and monitored by the study staff.

### **9.1.19 Patient Reported Outcome Measures**

Subjects will complete the IBDQ and EQ-5D health related QOL questionnaires at the time points specified in the schedule of events. Subjects will also complete the WPAI:CD to assess the impact on loss of work productivity and activity impairment.

#### ***9.1.19.1 Inflammatory Bowel Disease Questionnaire***

The IBDQ is a valid and reliable [\[30\]](#) 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.

#### *9.1.19.2 EQ-5D Questionnaire*

The EQ-5D questionnaire, developed by EuroQol, is a simple, valid, and reliable [31,32] instrument used to measure general health-related quality of life in patients and includes five domain items - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients choose the level of health problems they currently have on each item as “None”, “Moderate”, or “Extreme” and are scored a 1, 2, or 3, respectively. A composite EQ-5D score can be calculated from the individual scores to assess overall HRQOL. The EQ-5D VAS score is a self-assigned rating of overall health using a 20 cm visual, vertical scale, with a score of 0 as the worst and 100 as best possible health. The EQ-5D total score and EQ-5D VAS score have been shown in many studies to be valid and reliable instruments for measuring HRQOL in patients with GI diseases.

#### *9.1.19.3 Work Productivity and Activity Impairment-CD*

The WPAI questionnaire is a valid and reliable [33,34] 6-item instrument that consists of four metrics: absenteeism (the percentage of work time missed because of one’s health in the past seven days), presenteeism (the percentage of impairment experienced while at work in the past seven days because of one’s health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one’s health in the past seven days). The sum of specific health problem impairment and impairment due to other health reasons is equal to impairment due to all health reasons. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. WPAI-CD is the specific disease version of the questionnaire.

### **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 <specify reason>.
- Study termination.

- Other <specify reason>.

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

### **9.1.21 Documentation of Study Entrance**

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

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

## **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 re instructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

## **9.3 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).

### **9.3.1 Screening**

Subjects will be screened within 28 days prior to enrollment. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section [7.0](#). See Section [9.1.20](#) for procedures for documenting screening failures.

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

### **9.3.2 Enrollment**

Enrollment 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 enrolled using the IVRS/IWRS. 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](#).

### **9.3.3 Final Visit or Early Termination**

The Final Visit will be performed on Week 52 or at ET. Subjects who are not participating in the 26-week treatment extension (Part B) will have the Final Visit performed at Week 26.

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

#### **9.3.4 Postdose 18-Week Safety Follow-up**

Upon receipt of the last dose of study drug (completers and ETs), all subjects not transitioning into the XAP study will complete a safety follow-up visit 18 weeks postdose.

Assessments will be completed per the schedule of events for the Postdose 18-week Safety Follow-up visit.

Subjects who transition into the XAP study do not need to attend the Postdose 18-week Safety Follow-up Visit in MLN0002-3028. The safety of these subjects will be monitored as part of the XAP study.

#### **9.3.5 Poststudy Long-term Follow-up**

Upon completion of or early termination from the study, all subjects not transitioning into the XAP study will participate in a 6-month follow-up safety questionnaire. The questionnaire will be administered at 6 months from the last dose of study drug.

Subjects who transition into the XAP study do not need to take part in the Poststudy Long-term Follow-up survey in MLN0002-3028. The safety of these subjects will be monitored as part of the XAP study.

#### **9.3.6 Poststudy 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.

Subjects will have the option to transition to the XAP study for continued access to vedolizumab provided that:

1. Vedolizumab is not currently available to the subject through commercial channels, including reimbursement for the subject's particular clinical scenario, and
2. In the opinion of the investigator, the subject will continue to derive benefit from vedolizumab and continued treatment with vedolizumab is desired because there is no other comparable product available, or the subject may be expected to develop worsening of disease if they were to modify treatment.

#### **9.3.7 Unscheduled Visits Due to Disease Exacerbation**

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

- Physical examination.
- Vital Signs assessment.
- Diary review.
- Neurological examination.

- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Clinical chemistry and hematology, as indicated.
- CDAI.
- AVA sample collection.

There is no minimum time for repeat evaluation by unscheduled visit in order to determine if a subject meets the criteria for disease worsening. In general, however, enough time should be provided for clinically meaningful change to occur (eg, 1 week).

#### **9.4 Biological Sample Retention and Destruction**

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.14. 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.

#### **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. Is 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**

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

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 nonserious) 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: for subjects who do not transition into the XAP study AEs must be collected for 18 weeks following the last dose of study medication. If the subject is transitioned into the XAP study AEs must be collected until the Final Visit, Week 52.

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 for subjects not transitioning into the XAP study. For subjects who transition into the XAP study, routine collection of AEs will continue until the Final Visit, Week 52.

#### *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.

Several QOL instruments will be used in this study (eg, IDBQ, EQ5D, WPAI:CD). They 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*

Crohn’s Disease 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. These characteristics of disease activity will be regularly captured in the CDAI.

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 CD) 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, which 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 SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

#### **Hypersensitivity Reactions**

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 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, etc. that may represent an infusion-related reaction to study medication. If signs or symptoms of infusion-related reaction are observed during the administration of study drug, 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 infusion-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 infusion-related reactions should be discussed with the Medical Monitor.

#### **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 vedolizumab 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 vedolizumab 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 patient withdrawn from the study.

## **Infection**

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](#).

## **Malignancy**

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

## **Other**

Other special interest AEs include hepatotoxicity and PML, which are discussed in Sections [10.2.3](#) and [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 (LFTI) 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 LFTI eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

### 10.3 Follow-up of SAEs

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

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

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

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

## **11.0 STUDY-SPECIFIC COMMITTEES**

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

### **11.1 Adjudication Committee**

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

#### **11.1.1 Risk 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 [24,25]. Natalizumab is a pan- $\alpha_4$  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 [26,27]. In contrast, vedolizumab binds to the  $\alpha_4\beta_7$  integrin only [20] 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.

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## **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)**

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 eCRFs. 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. Data are transcribed directly onto eCRFs.

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.

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), 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

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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 database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

#### **13.1.1 Analysis Sets**

The Part A analyses will be performed on the following analysis sets:

- The full analysis set (FAS) will include all enrolled subjects who receive at least 1 dose of study drug.
- The FAS-MREn is the FAS within the MREn substudy.
- The modified full analysis set (mFAS) is a subset of the FAS and consists of all subjects who do not violate the terms of the protocol in a way that would impact the study outcome significantly.
- The per protocol analysis set (PPS) is a subset of the FAS and consists of all subjects who do not deviate the terms of the protocol in a way that would impact the study outcome significantly.

The Part B analyses will be performed on the following analysis sets:

- The FAS-Extension is the subset of subjects in the FAS who continue into Part B.
- The FAS-MREn-Extension is the subset of subjects in the FAS-MREn who continue into Part B.
- The mFAS-Extension is the subset of subjects in the mFAS who continue into Part B.
- The PPS-Extension is the subjects of subjects in the PPD who continue into Part B.

Significant protocol violations and significant protocol deviations will be identified prior to database lock.

The FAS and FAS-Extension will be used in both efficacy and safety analyses. The FAS-MREn and FAS-MREn-Extension will be used in the MREn analyses. Analyses using mFAS, mFAS-Extension, PPS, and PPS-Extension populations may be provided as sensitivity analyses. Sensitivity analyses using PPS/PPS-Extension will be conducted only if more than 15% of the subjects in the FAS/FAS-Extension have at least 1 significant protocol deviation.

#### **13.1.2 Analysis of Demographics and Other Baseline Characteristics**

Demographic and baseline characteristics will be summarized. 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 proportion-based efficacy endpoints will be summarized by presenting the point estimate and 95% confidence intervals for the proportion. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

All change from baseline efficacy endpoints will be summarized descriptively by time point.

The correlation between change from Baseline in CDAI, change from Baseline in SES-CD, change from Baseline in MaRIA, and change from Baseline in histology score will be explored. The relationship between SES-CD and MREn-based indices will be assessed at both the subject and intestinal segment levels. The relationship between the various remission statuses as defined by CDAI, endoscopic, imaging, and histological assessments will also be explored.

Change from baseline in QOL measures will be summarized descriptively overall and also by endoscopic remission status.

### **13.1.4 Pharmacogenomic Analysis**

In the event that pharmacogenomic analysis is undertaken, the following will apply.

- RNA / DNA-profiling and testing from tissues.

Further details will be outlined in the Pharmacogenomics Statistical Analysis Plan.

### **13.1.5 Other Analysis**

The proportion of subjects with positive AVA and proportion of subjects with positive neutralizing AVA during the study will be summarized. The impact of AVA on efficacy and safety may be explored.

### **13.1.6 Safety Analysis**

Safety analysis will be performed using the FAS.

The number and percentage of subjects with treatment-emergent adverse events (treatment-emergent adverse events [TEAEs]; defined as any AEs, regardless of relationship to study drug), AEs of special interest (ie, PML, malignancies, infusion reactions, infection, hypersensitivity, leukopenia, lymphopenia, hepatotoxicity), AEs leading to discontinuation, and SAEs that occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug, or until the Final Visit, Week 52 (if the subject is transitioned into the XAP study), will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by severity, and by relationship to study drug. Separate summaries will also be generated for treatment-related AEs overall and by severity.

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

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

### **13.2 Interim Analysis and Criteria for Early Termination**

Three interim analyses will be conducted for final efficacy at Weeks 14, 26 and 52, and for safety. Further details about the endpoints to be analyzed at each interim analysis will be outlined in the SAP.

### **13.3 Determination of Sample Size**

A sample size of 100 subjects will be sufficient to provide a 95% confidence interval based on normal approximation for the primary endpoint (endoscopic remission rate at Week 26) that extends no more than 10% in each direction from the estimated rate.

## 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. Significant protocol deviations will be entered into the eCRF, which is reviewed by the study sponsor or designee.

### 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 ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

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

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

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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 eCRF).

### **15.4 Publication, Disclosure, and Clinical Trial Registration Policy**

#### **15.4.1 Publication and Disclosure**

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

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

#### **15.4.2 Clinical Trial Registration**

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

Study Day/Week:	Screening	Treatment											Final Visit or ET	Postdose Follow-up visit (p)
		Part A							Part B					
	Days -28 to -1	Day 1	Week 2	Week 6	Week 10	Week 14	Week 22	Week 26 (a)	Week 30	Week 38	Week 46	Week 52	18-week Safety Follow-up	
Visit Windows (Days):			±3	±3	±3	±7	±3	±7	±7	±7	±7	±7	±7	±7
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13	
Informed consent	X													
Inclusion/exclusion criteria	X	X (b)												
Demographics /medical and medication history/ concurrent medical conditions	X													
CD prior biologics history (c)	X													
Physical examination	X	X (b)		X (b)	X	X (b)		X	X (b)	X(b)	X (b)	X	X	
Vital Signs	X	X (b)	X (g)	X (b)		X (b)	X (b)	X	X(b)	X(b)	X(b)	X	X	
Height and weight (d)	X	X		X	X	X		X	X	X	X	X	X	
CDAI	X (e)	X (f)		X (f)	X	X (f)		X(f)		X(f)	X	X(f)		
Patient diary	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ileocolonoscopy (g)	X					X		X					X	
MREn (h)	X							X					X	
<b>Sample Collection:</b>														
Fecal calprotectin (i)	X					X		X		X		X		
Tuberculosis screening (j)	X													
Hematology	X (k)	X (b)		X (b)	X	X(b)		X		X(b)		X	X	

Footnotes are on last table page.

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**Appendix A Schedule of Events (continued)**

Study Day/Week:	Screening	Treatment											Final Visit or ET	Postdose Follow-up visit (p)	
		Part A								Part B					
		Days -28 to -1	Day 1	Week 2	Week 6	Week 10	Week 14	Week 22	Week 26 (a)	Week 30	Week 38	Week 46	Week 52		
Visit Windows (Days):			±3	±3	±3	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7
Visit Number:	1	2	3	4	5	6	7	8	9	10	11	12	13		
Clinical chemistry	X (k)	X (b)							X		X(b)			X	X
Serum creatinine (for MREN)								X (l)					X(l)		
Urinalysis	X								X					X	
AVA		X (b)							X					X	X
CRP	X	X (b)			X				X		X			X	
Pharmacogenomic DNA and RNA samples (m)		X (b)													
Pregnancy testing (n)	X	X (b)	X (b)	X (b)	X	X (b)	X (b)	X	X (b)	X (b)	X (b)	X (b)	X	X	
QOLs		X (b)				X (b)		X		X			X		
WPAI:CD		X (b)				X (b)		X		X (b)			X		
ECG	X														
Dosing (IV)		X	X	X		X	X		X	X	X	X			
PML Checklist (b)	X	X	X	X	X	X	X	X	X	X	X	X			X
PML Wallet Card		X							X (o)					X (o)	
Concomitant medications / procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PTE assessment	X	X(b)													
AE/SAE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

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- (a) Week 26 is the final visit for subjects completing at Week 26 (Part A) and for subjects who continue to extension of treatment (Part B) this is a standard visit.
- (b) Assessment completed or sample taken pre-dose.
- (c) Collect prior biologic medications that stopped prior to screening.
- (d) Height collected only at the Screening Visit.
- (e) The components of the CDAI score to determine eligibility must be completed within 14 days prior to enrollment using hematocrit results collected during Screening.
- (f) CDAI score components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components.
- (g) Biopsies to be collected at Screening, Week 26, and Week 52/ET for those completing the study.
- (h) MREn conducted only at pre-identified sites. During the Screening period MREn should be performed prior to ileocolonoscopy. At Week 26 and Week 52 MREn to be performed prior to ileocolonoscopy either on the same day or at least 7 days before the ileocolonoscopy within the permitted time window for Week 26 or Week 52 procedures. Sites participating in MREn will need to check eGFR prior to procedure at Screening, Week 26, and Week 52 (using eGFR calculated from the Week 22 Visit for the Week 26 MREn and from the Week 46 Visit for the Week 52 MREn).
- (i) Stool sample to be collected and sent to central laboratory for evaluation of fecal calprotectin.
- (j) QuantiFERON® test or tuberculin skin test only.
- (k) Hepatitis and HIV testing only done at the Screening Visit.
- (l) Only subjects participating in MREn to have a sample for serum creatinine collected at Week 22 and Week 46. Samples will be sent to central laboratory for evaluation of eGFR.
- (m) DNA and RNA samples will be collected on Day 1 only for subjects that have consented to the Pharmacogenomic study.
- (n) Serum pregnancy completed at Screening and at the Postdose 18-week Safety Follow-up Visit (where applicable); urine pregnancy to be completed at other visits.
- (o) Long-term Follow-up Wallet card will be given to subjects at the last clinical visit.
- (p) Not required for subjects transitioning from MLN0002-3028 into the XAP study.

## **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 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject’s medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject’s personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject’s legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including (e)CRFs, 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.

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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 Crohn's Disease Activity Index (CDAI)

Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		× 2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe (reported on the 7 days immediately prior to the study visit)		× 5	
General well being	7-day total of daily general well-being scores on a 4-point scale: 0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible (reported on the 7 days immediately prior to the study visit)		× 7	
Extra-intestinal manifestations of Crohn's Disease	<p>Total number of checked boxes (check <b>all</b> that apply):</p> <p><input type="checkbox"/> Arthritis/arthralgia</p> <p><input type="checkbox"/> Iritis/uveitis</p> <p><input type="checkbox"/> Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis</p> <p><input type="checkbox"/> Anal fissure, fistula, or abscess</p> <p><input type="checkbox"/> Other fistula</p> <p><input type="checkbox"/> Fever over 37.8°C during past week</p>		× 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		× 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		× 10	
Hematocrit (%) (a)	Males: subtract value from 47 Females: subtract value from 42		× 6	
Body Weight (b)	(1 – (Body weight/Standard Weight)) × 100		× 1	
Final Score			Add totals:	

Source: Adapted from: Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70 (3):439-44 [35].

(a) If hematocrit subtotal < 0, enter 0.

(b) If body weight subtotal < -10, enter -10.

## **Appendix F Simple Endoscopic Score for Crohn's Disease (SES-CD)**

*Simplified endoscopic activity score for Crohn's disease: the SES-CD*

*M Daperno, G D'Haens, G Van Assche, et al.*

**Table 1. Definitions of Simple Endoscopic Score for Crohn's Disease**

Variable	Simple Endoscopic Score for Crohn's Disease values			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Ø, Diameter.

Source: Adapted from Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60(4):505-12 [36].

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## **Appendix G Collection, Storage, and Shipment of Pharmacogenomic Samples**

### **Instructions for processing and shipping of plasma samples for DNA pharmacogenomics**

1. Collect two tubes of venous blood (3 mL per tube) into a plastic tube containing K<sub>2</sub>EDTA.
2. Mix immediately by gently inverting the tube several times (at least 8-10 times) to mix the additive with the collected blood.
3. Freeze immediately at -70°C until shipment. If a -70°C freezer is not available, freeze immediately at -20°C.
4. Ship samples frozen on dry ice with preprinted air-bill per the instructions in the laboratory manual.

### **Instructions for processing and shipping of whole blood samples for RNA pharmacogenomics**

1. Ensure that the PAXGene™ Blood RNA Tube is at room temperature prior to collection.
2. Collect the venous blood into 2 plastic PAXGene™ Blood RNA 2.5 mL tubes for each timepoint.
3. Mix immediately by gently inverting the tube several times (at least 8-10 times) to mix the additive with the collected blood.
4. Keep tubes on ice while collecting then store in refrigerator (2-8°C) for up to 3 days.
5. Then freeze at -70°C until shipment. If a -70°C freezer is not available, freeze at -20°C.
6. Ship samples frozen on dry ice with preprinted air-bill per the instructions in the laboratory manual.

The storage provider has validated procedures in place for transport, delivery, retention, retrieval, and destruction of the specimens, and will appropriately retain the specimens for up to but not longer than 15 years as required by applicable law.

## Appendix H Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 05 are indicated. The corresponding text has been revised throughout the protocol.

**Change 1:** Allow all subjects (who complete Part B) in countries where vedolizumab is either not commercially available or is not reimbursed, continued access to vedolizumab by transition into an Extended Access Program (XAP), Vedolizumab-4013.

The primary change occurs in Section 6.1 Study Design

Added text: **Subjects who consent to Part B will have the option to voluntarily enroll into an XAP study after the Final Visit or Week 52 of MLN0002-3028. Subjects who transition into the XAP study will not take part in the 18-week follow-up period or the 6-month safety follow-up telephone call following their last dose in MLN0002-3028. The end of trial will be the Week 52 visit for these subjects and the duration of the study will be approximately 56 weeks.**

### Rationale for Change:

Allow all subjects (who complete Part B) in countries where vedolizumab is either not commercially available or is not reimbursed, continued access to vedolizumab by transition into an XAP, Vedolizumab-4013.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Figure 6.b Schematic of Study Design: For Subjects on 52 Weeks of Treatment.
- Section 9.1.11 Pregnancy.
- Section 9.3.6 Poststudy Care.
- Section 13.1.6 Safety Analysis.
- Appendix A Schedule of Events.

**Change 2:** Remove the requirement for subjects who transition into the XAP study to attend the 18-week Safety Follow-up Visit in the MLN0002-3028 study. The safety of these subjects will be monitored as part of the XAP study.

The primary change occurs in Section 6.1 Study Design

---

Added text: **Subjects who consent to Part B will have the option to voluntarily enroll into an XAP study after the Final Visit or Week 52 of MLN0002-3028. Subjects who transition into the XAP study will not take part in the 18-week follow-up period or the 6-month safety follow-up telephone call following their last dose in MLN0002-3028. The end of trial will be the Week 52 visit for these subjects and the duration of the study will be approximately 56 weeks.**

---

**Rationale for Change:**

Remove the requirement for subjects who transition into the XAP study to attend the 18-week Safety Follow-up Visit in the MLN0002-3028 study. The safety of these subjects will be monitored as part of the XAP study.

---

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 5.2.3 Additional Endpoints.
- Figure 6.b Schematic of Study Design: For Subjects on 52 Weeks of Treatment.
- Section 9.3.4 Postdose 18-Week Safety Follow-up.
- Appendix A Schedule of Events.

---

**Change 3:** Remove the requirement for subjects who transition into the XAP study to participate in the 6-month long-term follow-up safety questionnaire in the MLN0002-3028 study. The safety of these subjects will be monitored as part of the XAP study.

---

The primary change occurs in Section 6.1 Study Design

---

Added text: **Subjects who consent to Part B will have the option to voluntarily enroll into an XAP study after the Final Visit or Week 52 of MLN0002-3028. Subjects who transition into the XAP study will not take part in the 18-week follow-up period or the 6-month safety follow-up telephone call following their last dose in MLN0002-3028. The end of trial will be the Week 52 visit for these subjects and the duration of the study will be approximately 56 weeks.**

---

**Rationale for Change:**

Remove the requirement for subjects who transition into the XAP study to participate in the 6-month long-term follow-up safety questionnaire in the MLN0002-3028 study. The safety of these subjects will be monitored as part of the XAP study.

---

---

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Figure 6.b Schematic of Study Design: For Subjects on 52 Weeks of Treatment.
- Section 9.3.5 Poststudy Long-term Follow-up.
- Appendix A Schedule of Events.

---

**Change 4:** Amend the adverse event, serious adverse event, and concomitant medication reporting instructions for subjects who transition into the XAP study, such that the MLN0002-3028 collection period ends at the time the subject is consented into the XAP.

---

The primary change occurs in Section 10.2.1.1 PTE and AE Collection Period

Formerly read:

- 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.

---

Now reads:

- Start of AE collection: AEs must be collected from start of study medication administration.
- End of AE collection: **for subjects who do not transition into the XAP study** AEs must be collected for 18 weeks following the last dose of study medication. **If the subject is transitioned into the XAP study AEs must be collected until the Final Visit, Week 52.**

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 **for subjects not transitioning into the XAP study. For subjects who transition into the XAP study, routine collection of AEs will continue until the Final Visit, Week 52.**

---

#### Rationale for Change:

Amend the adverse event, serious adverse event, and concomitant medication reporting instructions for subjects who transition into the XAP study, such that the MLN0002-3028 collection period ends at the time the subject is consented into the XAP.

---

#### Change 5: Administrative change to the Responsible Medical Officer.

---

The primary change occurs in Section 1.1 Contacts

Formerly  
read:

PPD



---

Now reads:

PPD



---

**Rationale for Change:**

Administrative change to the Responsible Medical Officer.

---

Section [1.2 Administrative information](#) also contains this change.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD		28-Nov-2016 18:38 UTC
		29-Nov-2016 09:23 UTC