



Title: Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

NCT Number: NCT02611817

Protocol Approve Date: 24 August 2017

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## PROTOCOL

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

### Efficacy and Safety of Vedolizumab SC as Maintenance Therapy in Crohn's Disease

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**Study Number:** MLN0002SC-3031

**IND Number:** 118980      **EudraCT Number:** 2015-000481-58

**Compound:** Vedolizumab SC

**Date:** 24 August 2017      **Amendment Number:** 06

#### Amendment History:

Date	Amendment Number	Amendment Type	Region
26 February 2015	Initial Protocol	Not applicable	Global
12 October 2015	01	Substantial	Global
10 February 2016	02	Substantial	Global
12 May 2016	03	Substantial	Global
28 July 2016	04	Substantial	Global
28 September 2016	05	Substantial	Japan
24 August 2017	06	Substantial	Global

## 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.

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Contact Type/Role	Americas, Europe, Asia and Japan TDC Contact
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol and compound) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

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## 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 can be found on the signature page.

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

PPD



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## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure or package insert as applicable, 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 life, dignity, integrity, confidentiality of personal information, rights, safety, privacy, and well-being of study subjects in accordance with the following:

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

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

---

Signature of Investigator

Date

---

Investigator Name (print or type)

---

Investigator's Title

---

Location of Facility (City, State/Province)

---

Location of Facility (Country)

### 1.3 Protocol Amendment 06 Summary of Changes

#### Rationale for Amendment No. 06

This document describes the changes in reference to the Protocol Incorporating Amendment No. 06.

The primary reason for this amendment is to include a pre-Week 14 visit and to clarify the Week 14 procedures for subjects who enroll and do not enroll into the open-label extension (OLE) study (MLN0002SC-3030). Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see [Appendix H](#).

#### Changes in Amendment 06

1. Clarification of the Sponsor address in Japan.
2. Administrative change to the Responsible Medical Officer and Approvers.
3. Inclusion of an additional secondary objective and endpoint, and exploratory endpoint.
4. Clarification to the Final Visit/Early Termination procedures for subjects who complete (OLE Enroller/Nonenroller) at Week 14 (Induction Phase), and subjects who complete (Week 52) or discontinue from the Maintenance Phase.
5. Clarification to the study design schematic.
6. Study design updated to clarify that all endoscopies will be centrally read.
7. Clarification to Inclusion Criterion #11.
8. Clarification to Exclusion Criterion #5.
9. Clarification to Exclusion Criterion #15.
10. Clarification to Exclusion Criterion #20.
11. Clarification to the period for excluded medications and treatments.
12. Clarification to Section 9.1.5 Vital Signs Procedure.
13. Clarification to Section 9.1.6.1 Diary Completion and Review.
14. ECG procedure updated.
15. Addition of a Pre-Week 14 visit for Week 6 nonresponders.
16. Update to [Appendix A](#) Schedule of Study Procedures for Crohn's disease-related events.
17. Update to [Appendix B](#) Responsibilities of the Investigator.

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## 2.0 STUDY SUMMARY

<b>Name of Sponsor(s):</b> Takeda Development Center Americas, Inc. Takeda Development Centre Europe, Ltd. Takeda Development Center Asia, Pte. Ltd. Takeda Pharmaceutical Company, Ltd.	<b>Compound:</b> Vedolizumab SC	
<b>Title of Protocol:</b> A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy	<b>IND No.:</b> 118980	<b>EudraCT No.:</b> 2015-000481-58
<b>Study Number:</b> MLN0002SC-3031	<b>Phase:</b> 3	
<b>Study Design:</b> This is a pivotal, phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab subcutaneous (vedolizumab SC) in adult subjects with moderately to severely active Crohn's Disease (CD) who achieved a clinical response at Week 6 with open-label therapy with 300 mg vedolizumab intravenous (vedolizumab IV) at Weeks 0 and 2. Subjects that are either tumor necrosis factor-alpha (TNF- $\alpha$ ) antagonist naïve or with TNF- $\alpha$ antagonist failure will be included, ensuring approximately 50% of subjects with TNF- $\alpha$ antagonist failure are enrolled. Subjects with previous use of TNF- $\alpha$ antagonist but not failed will be included ensuring that no more than 10% of such subjects are enrolled. CCI		
<b>Primary Objectives:</b> To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active CD who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.		
<b>Secondary Objectives:</b> <ul style="list-style-type: none"><li>To assess the effect of vedolizumab SC maintenance treatment on enhanced clinical response at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.</li><li>To assess the effect of vedolizumab SC maintenance treatment on corticosteroid-free remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.</li><li>To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects who are naïve to TNF-<math>\alpha</math> antagonist exposure and achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.</li></ul>		
<b>Select Exploratory Objectives:</b> <ul style="list-style-type: none"><li>CCI</li></ul>		

<b>Subject Population:</b> Adult subjects with CD, aged 18 to 80 years inclusive.	
<b>Number of Subjects:</b> Approximately 824 subjects enrolled to enable approximately 387 subjects to be randomized for maintenance treatment.	<b>Number of Sites:</b> Approximately 240 sites globally
<b>Dose Level(s):</b> Vedolizumab SC, 108 mg. Vedolizumab IV, 300 mg.	<b>Routes of Administration:</b> Subcutaneous Intravenous
<b>Duration of Treatment:</b> 52-week treatment period	<b>Period of Evaluation:</b> The study includes a 4-week (28-day) Screening Period, a 6-week open-label vedolizumab IV Induction Phase, and a 46-week randomized, double-blind, placebo-controlled Maintenance Phase with vedolizumab SC with a final visit at Week 52. Subjects who do not participate in the open-label extension (OLE) study will be required to participate in a Final Safety Visit 18-weeks after the last study drug dose and a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.
<b>Main Criteria for Inclusion:</b> The subject has a diagnosis of CD established at least 3 months prior to screening, by clinical and endoscopic evidence and corroborated by a histopathology report. The subject has moderately to severely active CD. The subject has CD involvement of the ileum and/or colon, at a minimum. The subject has demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents: immunomodulators, corticosteroids, or TNF- $\alpha$ antagonists.	
<b>Main Criteria for Exclusion:</b> The subject has had extensive colonic resection, subtotal or total colectomy. The subject has a history of >3 small bowel resections or diagnosis of short bowel syndrome. The subject has any evidence of an active infection during Screening. The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective checklist at Screening (or at Week 0 before the administration of study drug). The subject has received any investigational or approved biologic or biosimilar within 60 days or 5 half-lives, of screening, whichever is longer. The subject has had prior exposure to vedolizumab. The subject has had prior exposure to natalizumab, efalizumab, etrolizumab, AMG-181, anti-mucosal addressin cell adhesion molecule-1(MAdCAM-1) antibodies, or rituximab.	

**Main Criteria for Evaluation and Analyses:**

The primary endpoint for this study is the proportion of subjects with clinical remission, defined as CDAI score  $\leq 150$ , at Week 52.

Secondary endpoints for this study are:

- Proportion of subjects with enhanced clinical response, defined as a  $\geq 100$  point decrease in CDAI score from Baseline (Week 0), at Week 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
- Proportion of TNF- $\alpha$  antagonist naïve subjects who achieved clinical remission, defined as CDAI score  $\leq 150$ , at Week 52.

Select exploratory endpoints for this study:

CCI



**Statistical Considerations:**

All statistical testing will be performed at 2-sided 0.05 level of significance. To control the overall Type I error rate for the primary and secondary endpoints, the statistical inference for the first secondary endpoint of enhanced clinical response will only be performed if the primary endpoint is statistically significant. The second secondary endpoint of corticosteroid-free clinical remission will only be tested if the first secondary endpoint is statistically significant.

All dichotomous efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel tests for risk differences, stratified by randomization stratum. All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis.

**Sample Size Justification:**

Assuming a clinical remission rate of 38% for vedolizumab and 22% for placebo at Week 52, a sample size of 258 subjects in the vedolizumab SC group and 129 subjects in the placebo group will provide 90% power at 2-sided 0.05 level of significance. To ensure a randomized sample size of 387 subjects, assuming 47% of the subjects entering induction will achieve clinical response at Week 6, approximately 824 subjects will need to be enrolled into the study.

### **3.0 STUDY REFERENCE INFORMATION**

#### **3.1 Study-Related Responsibilities**

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

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites (and, if applicable, investigators and/or other study staff) will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor prior to the start of the study at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

#### **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.

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### 3.3 List of Abbreviations

Term	Definition
5-ASA	5-aminosalicylate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCI	
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
C <sub>max</sub>	maximum observed serum concentration
CNS	central nervous system
CRP	C-reactive protein
C <sub>trough</sub>	trough serum concentration levels
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EPX	E-Pro eXchange
EQ-5D	Euro Quality of Life-5D
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal(ly)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	healthcare provider
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IM	intramuscular(ly)

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<b>Term</b>	<b>Definition</b>
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
JCV	John Cunningham virus
LFT	liver function test
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PC	product complaint
CCI	
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PRO	patient-reported outcome
PTE	pretreatment event
PVC	polyvinyl chloride
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
QOL	quality of life
RAMP	Risk Assessment and Management Program for PML
SAE	serious adverse event
SAP	statistical analysis plan

CCI

SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF- $\alpha$	tumor necrosis factor- alpha
UC	ulcerative colitis
ULN	upper limit of normal
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1
WBC	white blood cell

CCI

### 3.4 Corporate Identification

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

### 3.5 Study Definitions

Term	Definition
Clinical remission by	A Crohn's Disease Activity Index (CDAI) score $\leq 150$ .

CCI

Corticosteroid-free remission	Subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
Disease worsening	A $\geq 100$ point increase in CDAI score from the Week 6 value on 2 consecutive visits and a minimum CDAI score of 220 points.
Durable clinical remission	Clinical remission at Week 6 and Week 52.
Enhanced clinical response	A $\geq 100$ point decrease in CDAI score from Baseline (Week 0).
Treatment failure	Defined as disease worsening, need for rescue medications (as defined in Section 7.3.1), or need for surgical intervention for treatment of Crohn's Disease.

## 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 a relapsing, remitting inflammatory disease that may involve any portion of the length of the GI tract from mouth to anus in a transmural fashion from mucosa to serosa. The prevalence of CD is approximately 150/100,000 of the US population and approximately 125/100,000 of population in Western Europe [1-3] and 21.2/100,000 of the population in Japan [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 histopathologic examination of endoscopic mucosal biopsy specimens obtained on ileocolonoscopy.

Because in CD, clinical manifestations are not necessarily correlated with endoscopic and radiographic findings of disease activity [5], and as further evidence has emerged on the predictive potential of endoscopic improvement on long term clinical outcomes [6-8] endoscopic assessments have been incorporated in clinical studies for therapeutic outcomes evaluation. Currently, limited endoscopic data in CD patients exists and are inconsistent due to lack of a validated definition of endoscopic mucosal healing, guidelines for scoring mucosal lesions and for the appropriate timing of assessment, as well as of cutoff values for disease severity and response to therapy [9,10]. CCI



Current treatments have been effective for many patients with CD but have numerous limitations for patients with moderately to severely active disease. The National Cooperative Crohn's Disease Study demonstrated a role for sulfasalazine (a 5-aminosalicylate [5-ASA]) in moderately to severely active CD [11]. However, the efficacy of 5-ASAs in CD has been called into question by a recent meta-analysis [12].

Corticosteroids are often required for the 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 due to 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 [13].

Methotrexate 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.

Biologic agents, including monoclonal antibodies (mAbs) against tumor necrosis factor-alpha (TNF- $\alpha$ ), such as infliximab (Remicade), adalimumab (Humira) and certolizumab pegol (Cimzia), have proven useful for both induction and maintenance of clinical response and clinical remission in CD [14-16]. However, efficacy data for both infliximab and adalimumab in CD indicate only a minority of patients having a durable response at 1 year [17,18]. Certolizumab pegol as maintenance therapy was studied only up to 26 weeks, and achieves the same modest results in the general moderately to severely active CD population with more substantial outcomes in the subgroup of patients with baseline C-reactive protein (CRP)  $\geq 10$  mg/L [19,20]. In addition to its modest efficacy, treatment with TNF- $\alpha$  antagonists has been associated with serious adverse events (SAEs) involving hypersensitivity and infection. Reactivations of latent tuberculosis (TB) [21] and disseminated histoplasmosis have been reported and, in some cases, have been fatal [22]. A new class of therapy, the integrin inhibitors, has shown promising results to date. Integrin antagonists target and disrupt the leukocyte adhesion and trafficking systems, thereby reducing inflammation. Natalizumab (Tysabri), a pan- $\alpha_4$  ( $\alpha_4\beta_7$  and  $\alpha_4\beta_1$ ) integrin antagonist was approved by the Food and Drug Administration (FDA) in 2008 for use in CD patients who are refractory to standard therapy [23]. However, due to the antagonizing effect of natalizumab on  $\alpha_4\beta_1$ , which mediates T-cell migration into the central nervous system (CNS), bone marrow, and skin via adhesion to its ligand, vascular cell adhesion molecule-1 (VCAM1), natalizumab therapy has been associated with increased risk of John Cunningham virus (JCV) reactivation and subsequent development of progressive multifocal leukoencephalopathy (PML). As a result, natalizumab is cautiously prescribed for the treatment of CD.

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 [24]. The limitations of current therapies for IBD indicate that there is a significant need for safer and more effective therapies.

#### 4.1.2 Vedolizumab

Vedolizumab (also known as MLN0002) is a novel recombinant humanized mAb composed of 2 light chains of the  $\kappa$  subclass and 2 immunoglobulin G1 heavy chains. Vedolizumab binds specifically to 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 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 [25-28]. As a result, vedolizumab impairs the migration of gut-homing leukocytes into GI mucosa [29] and acts as a gut-selective immunomodulator.

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

Vedolizumab subcutaneous (SC) (also known as Vedolizumab Injection, for Subcutaneous Use; Vedolizumab Solution for Injection in Pre-filled Syringe; or MLN0002 SC) is a new liquid presentation that has been developed for SC administration. CCI

Therefore, the nonclinical and clinical information from studies with vedolizumab IV are considered relevant.

As of 19 May 2015 (data lock point), more than 3600 subjects have received at least 1 dose of vedolizumab across all studies in the clinical development program. Phase 3 placebo-controlled studies enrolled 2427 subjects with UC or CD, of whom 1434 subjects were administered 300 mg of vedolizumab IV 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 [30-32]. As of 19 May 2015, vedolizumab exposure has extended for  $\geq 12$  months in 1667 subjects,  $\geq 24$  months in 1306 subjects,  $\geq 36$  months in 935 subjects,  $\geq 48$  months in 676 subjects,  $\geq 60$  months in 267 subjects, and  $\geq 72$  months in 26 subjects. Based on the most recent drug shipment data (19 November 2015), the cumulative patient exposure to vedolizumab since its marketing approval in May 2014 is estimated to be approximately 25,831 patient-years.

Previously conducted clinical studies have characterized the efficacy, safety, tolerability, pharmacokinetic (PK), pharmacodynamic, and immunogenicity of vedolizumab in healthy subjects and subjects with UC or CD. Please refer to the current edition of the Investigator's Brochure (IB) for the most recent data for 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 [29].

A single-dose local tolerance study was conducted to determine the local irritancy potential of vedolizumab SC when administered by SC injection to rabbits. Macroscopic and histological examinations of the injection sites indicated no findings of concern with the vehicle or formulated vedolizumab SC.

#### 4.1.2.2 Clinical Experience With Vedolizumab IV

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

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 IV 300 mg at Weeks 0 and 2 (induction) followed by 300 mg either once every 4 weeks (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 (Table 4.a). 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 (Table 4.b) [31].

**Table 4.a Efficacy of Vedolizumab IV in Subjects With CD During the Induction Phase (Week 6, C13007)**

Endpoint	PBO N=148	VDZ N=220	Difference	p-value
<b>Primary endpoint</b>				
Clinical remission (%)	6.8	14.5	7.8	0.0206
Enhanced clinical response	25.7	31.4	5.7	0.2322

Source: C13007 Clinical Study Report.  
PBO=placebo, VDZ=vedolizumab.

**Table 4.b Efficacy of Vedolizumab IV in Subjects With CD During the Maintenance Phase (Week 52, C13007)**

Endpoint	PBO N=153	VDZ Q8W N=154	VDZ Q4W N=154	Difference Q8W vs PBO Q4W vs PBO	p-value
<b>Primary endpoint</b>					
Clinical remission (%)	21.56	39.0	36.4	17.4 14.7	0.0007 0.0042
<b>Secondary endpoint</b>					
Enhanced clinical response at Week 52 (%) (a)	30.1	43.5	45.5	13.4 15.3	0.0132 0.0053
Corticosteroid-free clinical remission at Week 52(%) (b)	15.9	31.7	28.8	15.9 12.9	0.0154 0.0450

Source: C13007 Clinical Study Report.

PBO=placebo, VDZ=vedolizumab.

(a) Enhanced clinical response is defined as a  $\geq 100$ -point reduction in CDAI score from Baseline.

(b) Corticosteroid-free clinical remission is defined as subjects using oral corticosteroids at Baseline who had discontinued corticosteroids and were in clinical remission at Week 52.

In Study C13011, vedolizumab IV (300 mg 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 IV were also demonstrated for the overall population and in the subgroup of subjects who were TNF- $\alpha$  antagonist naïve [32].

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 subjects), 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 IV 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 safety assessment is available for an ongoing long-term open-label extension (OLE) study (C13008), in which subjects are administered vedolizumab IV Q4W.

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 IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (SAEs) have been related to exacerbations or complications of the underlying UC or CD. For those infections that were reported more frequently in vedolizumab-treated subjects, the sites of these infections correlated with the known tissue



distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). A total of 4% of vedolizumab-treated subjects and 3% of placebo-treated subjects experienced an infusion-related reaction. In Studies C13006 and C13007, 10% of subjects were positive for antivedolizumab antibodies 16 weeks following the last dose of vedolizumab. Results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment. Overall, the safety profile following long-term treatment with vedolizumab IV in Study 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.

One death occurred in a vedolizumab-treated subjects during Study C13006, and 5 deaths occurred during Study C13007, including 1 death in a placebo-treated subject. As of 19 May 2015, a total of 26 deaths from multiple causes were reported in the vedolizumab clinical development program, including the ongoing long-term Study C13008. Twenty-five of the 26 subjects were randomized to the vedolizumab treatment group. Of these deaths, 14 occurred within 18 weeks of the last dose of study drug in phase 3 clinical studies, and 11 occurred more than 18 weeks after the last dose of vedolizumab was administered. The causes of death varied and detailed information can be found in the current edition of the IB.

Overall, vedolizumab was well tolerated in clinical studies.

#### 4.1.2.3 Clinical Experience With Vedolizumab SC

The feasibility of administering the vedolizumab IV formulation by alternative dosing routes SC or intramuscular (IM) injection was explored in an open-label, single dose, parallel-group bioavailability study (C13010) in healthy male subjects. In this study, 42 subjects were enrolled and 14 subjects each received a single dose of 180 mg vedolizumab IV as IV infusion (over 30 minutes), SC injections ( $2 \times 1.5 \text{ mL} \times 60 \text{ mg/mL}$ ), or IM injections ( $2 \times 1.5 \text{ mL} \times 60 \text{ mg/mL}$ ). Following SC administration, absorption of vedolizumab was gradual, achieving maximum concentration at 7 days post-injection (time to reach maximum serum concentration). The maximum observed serum concentration ( $C_{\text{max}}$ ) following SC injection was approximately 1/3 of the  $C_{\text{max}}$  following 30 minute IV infusion. There was no difference in the terminal elimination profile of the SC cohort compared to the IV cohort, indicating that the elimination of vedolizumab is not absorption rate-limited. The absolute bioavailability of vedolizumab was approximately 75% for SC administration. Vedolizumab was well tolerated when administered at a dose of 180 mg by SC injection. Five of the 14 subjects (36%) in the IV infusion cohort and 3 of the 14 subjects (21%) in the SC cohort experienced a drug-related AE (assessed by the investigator). Most AEs were mild or moderate in severity. Three of the 14 subjects (21%) in the IV infusion cohort and 2 of the 14 subjects (14%) in the SC cohort in this study were anti-vedolizumab antibody (AVA) positive using the originally developed AVA assay that was used in the phase 3

studies with vedolizumab IV. While all 3 AVA positive subjects in the IV infusion cohort had neutralizing AVA, no neutralizing AVA was observed in the SC cohort.

The bioavailability and PK of vedolizumab following a single SC injection of vedolizumab SC at 3 dose levels (54, 108, and 160 mg) relative to a single IV infusion of vedolizumab IV 300 mg was examined in a phase 1, open-label study (MLN0002SC-101). Forty-eight (24 Japanese and 24 non-Japanese) healthy, adult male and female subjects were randomized. A total of 12 subjects received a single dose of vedolizumab IV 300 mg and 36 subjects received a single dose of vedolizumab SC at 54, 108, or 160 mg (12 subjects per dose group).

The bioavailability following a single SC injection of vedolizumab SC was 75.1%, independent of the vedolizumab SC dose evaluated (54, 108, or 160 mg). Vedolizumab reached maximum serum concentrations around 1 week after a single SC injection. Vedolizumab was eliminated by both linear and nonlinear pathways following SC injection, with more rapid elimination with decreasing dose/concentration. Compared with non-Japanese subjects, Japanese subjects generally showed similar or slightly higher exposure; however, ethnicity did not have an impact on clearance or central volume of distribution based on the population PK analysis, likely due to the fact that weight was included as a covariate for various population PK parameters. Simulations further confirmed that vedolizumab SC at 108 mg every 2 weeks (Q2W) is expected to provide lower trough concentrations at steady state than vedolizumab IV 300 mg Q4W and similar steady-state exposures (average serum concentration at steady state) as the approved vedolizumab IV 300 mg Q8W maintenance regimen.

An electrochemiluminescence (ECL) assay has been developed to determine serum titers of AVA. This assay has improved drug tolerance as compared with the prior enzyme-linked immunosorbent assay (ELISA) method used in the vedolizumab clinical development program and, as a result, is more sensitive. Both assays were used in Study MLN0002SC-101; the ECL assay data were used in the analysis of PK and safety.

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Overall, 75.0% (36/48) of subjects had treatment-emergent adverse events (TEAEs), and the percentage of subjects with a TEAE was identical in subjects who received vedolizumab SC compared with subjects who received vedolizumab IV. All TEAEs were considered by the investigator to be mild or moderate in intensity; no TEAEs of severe intensity were reported. The percentage of subjects with mild or moderate TEAEs was similar between subjects who received vedolizumab SC and vedolizumab IV; the percentages were also similar across the dose groups. No subjects had clinical laboratory test results, vital signs, or electrocardiogram (ECG) results that

were reported as AEs. Two subjects had elevated bilirubin levels that met the predefined markedly abnormal value criteria; however, no subject had abnormal liver function test (LFT) results involving aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

Two AEs of special interest were reported: 1 subject in the vedolizumab SC 108 mg group experienced erythema at the injection site on the left thigh, and 1 subject in the vedolizumab SC 160 mg group experienced an injection site reaction. Both events occurred on Day 1 and were observed at the 30 minute postdose observation time point (a protocol-defined time point). In each case, the event resolved at the 1.5 hour postdose observation time point and was considered by the investigator to be mild in intensity and related to study drug. Both subjects recovered without any sequelae.

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No SAEs, severe AEs, or deaths were reported in Study MLN0002SC-101. The observed AEs are consistent with the overall safety profile of vedolizumab.

#### 4.2 Rationale for the Proposed Study

As IV infusion may not be convenient as long-term therapy for some patients, vedolizumab SC has been developed to enable injection by patients or their caregivers.

This phase 3 study is designed to evaluate the efficacy, safety, PK, and immunogenicity of multiple injections of the new presentation, vedolizumab SC, as maintenance therapy in subjects with CD.

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Therefore, all nonclinical and clinical information from studies with vedolizumab IV is considered relevant.

The vedolizumab exposure-efficacy relationship has been demonstrated in UC subjects in the phase 3 vedolizumab IV study (C13006), where higher serum vedolizumab concentrations were associated with higher efficacy (Source: Population PK Efficacy Report 2013). Although the exposure-efficacy relationship demonstrated in UC subjects was not as clear in CD subjects participating in the vedolizumab IV phase 3 studies, the vedolizumab SC dosing regimen selection is applicable to CD subjects based on the following important considerations:

- Vedolizumab targets the same mechanism of action in both the UC and CD indications.
- Vedolizumab IV was effective in inducing and maintaining remission in subjects with moderately to severely active UC or CD who had failed conventional and/or TNF- $\alpha$  antagonist therapy.

- No differences in PK, safety, or immunogenicity between the UC or CD subjects were observed in the vedolizumab IV phase 3 studies.

The proposed vedolizumab SC maintenance dosing regimen (108 mg Q2W) was selected to provide lower steady-state trough concentrations than the vedolizumab IV Q4W dosing regimen and similar  $C_{avg}$  steady-state exposures to that from the approved vedolizumab IV Q8W dosing regimen, and the safety and efficacy of the vedolizumab SC presentation are expected to be similar to those of vedolizumab IV, outside of expected local administration site events, such as injection-site reactions.

#### 4.3 Benefit:Risk Assessment

The proposed study (MLN0002SC-3031) is designed to evaluate the efficacy and safety of vedolizumab SC as maintenance therapy in subjects with moderately to severely active CD who achieved clinical response following open-label vedolizumab IV therapy. Because IV infusion may not be convenient as long-term therapy, vedolizumab SC has been developed to ultimately enable injection by patients or their caregivers. CCI

. Therefore, the nonclinical and clinical information from studies with vedolizumab IV are considered relevant.

The study population in Study MLN0002SC-3031 is consistent with the approved vedolizumab IV label. The proposed vedolizumab SC maintenance dosing regimen (108 mg Q2W) was selected to provide similar steady-state exposure to that from the approved vedolizumab IV dosing regimen (300 mg Q8W). It is expected that similar steady-state exposure to vedolizumab will result in similar maintenance efficacy, independent of the dosing route or presentation. In addition, safety of the vedolizumab SC presentation is expected to be similar to that of vedolizumab IV due to similar exposure, outside of expected local administration site events, such as injection-site reactions. CCI

The observed AEs with vedolizumab SC are consistent with the vedolizumab IV safety profile.

Overall, vedolizumab has been well tolerated in clinical studies, including a phase 1 study of vedolizumab SC, and has a positive benefit-risk profile in the treatment of CD.

## 5.0 STUDY OBJECTIVES AND ENDPOINTS

### 5.1 Objectives

#### 5.1.1 Primary Objective(s)

- To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active CD who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

#### 5.1.2 Secondary Objectives

- To determine the effect of vedolizumab SC maintenance treatment on enhanced clinical response at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To determine the effect of vedolizumab SC maintenance treatment on corticosteroid-free remission at Week 52 in subjects who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.
- To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects who are naïve to TNF- $\alpha$  antagonist exposure, and achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

#### 5.1.3 Exploratory Objectives

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## 5.2 Endpoints

### 5.2.1 Primary Endpoints

- Proportion of subjects with clinical remission, defined as CDAI score  $\leq 150$ , at Week 52.

### 5.2.2 Secondary Endpoints

- Proportion of subjects with enhanced clinical response, defined as a  $\geq 100$  point decrease in CDAI score from Baseline (Week 0), at Week 52.
- Proportion of subjects with corticosteroid-free remission, defined as subjects using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52.
- Proportion of TNF- $\alpha$  antagonist naïve subjects who achieved clinical remission, defined as CDAI score  $\leq 150$ , at Week 52.

### 5.2.3 PRO Endpoints

- Changes in inflammatory bowel disease questionnaire (IBDQ) total score and subscores, from Baseline (Week 0) to Week 52 and from Week 6 to Week 52.
- Changes in Euro Quality of Life-5D (EQ-5D) utility scores and EQ-5D visual analog scale (VAS) score from Baseline (Week 0) to Week 52 and from Week 6 to Week 52.

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#### 5.2.4 Exploratory Endpoints

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## 6.0 STUDY DESIGN AND DESCRIPTION

### 6.1 Study Design

This is a pivotal, phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC in adult subjects with moderately to severely active CD who achieved a clinical response at Week 6 with open-label therapy with 300 mg vedolizumab IV at Weeks 0 and 2.

Moderately to severely active CD is defined as described in Inclusion Criteria (Section 7.1). Subjects who are either TNF- $\alpha$  antagonist naïve or with TNF- $\alpha$  antagonist failure will be included ensuring approximately 50% of subjects with TNF- $\alpha$  antagonist failure are enrolled. Subjects with previous use of TNF- $\alpha$  antagonist but not failed will be included ensuring that no more than 10% of such subjects are enrolled.

The study includes a 4-week (28-day) Screening Period, a 6-week open-label vedolizumab IV Induction Phase, and a 46-week randomized, double-blind, placebo-controlled Maintenance Phase with vedolizumab SC with final visit at Week 52.

Eligible subjects will be enrolled into the Induction Phase at Week 0, will receive open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2, and will be assessed for clinical response by CDAI (defined as a  $\geq 70$  point decrease in CDAI score from Baseline [Week 0]) at Week 6, as follows:

- Subjects who achieve a clinical response at Week 6 will be randomized into the Maintenance Phase. Upon completion of the Week 52 assessment or upon early discontinuation due to treatment failure (ie, disease worsening after Week 6 or need for rescue medications after Week 14) these subjects will be eligible to enter the OLE study (Table 7.a).
- Subjects who do not achieve a clinical response at Week 6 will not be randomized in to the Maintenance Phase, and instead will receive a third infusion of vedolizumab IV 300 mg at Week 6. Subjects who achieve a clinical response at Week 14 (by CDAI) will be eligible to enroll in the OLE study. Subjects who respond but choose not to enroll in the OLE study and subjects who do not achieve clinical response at Week 14 will be discontinued.

Subjects who achieve a clinical response at Week 6 will be randomized at a 2:1 ratio to receive blinded injections of vedolizumab SC 108 mg or placebo SC Q2W, beginning at Week 6 through Week 50.

Randomization will be stratified by:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF- $\alpha$  antagonist failure/exposed or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

At Week 6, subjects receiving oral corticosteroids who achieved a clinical response and are randomized into the Maintenance Phase will begin a corticosteroid tapering regimen.

After receiving training from the health care provider (HCP; investigator or designee) on the proper SC injection technique and how to manage hypersensitivity reactions potentially associated with the injection, subjects or their caregivers will inject vedolizumab SC or placebo SC under the supervision of the HCP during at least the Week 6 and 8 clinic visits to ensure proper injection technique prior to home dosing. In addition, injection during clinic visits will allow for direct observation of any potential hypersensitivity or injection site reactions associated with SC injection and timely intervention by the HCP. Subjects and caregivers may attend the clinic at Weeks 10 and 12 if further training is required. Subjects or their caregivers will also administer SC injections during the scheduled clinic visits at Weeks 14, 22, 30, 38, 46, and 50 under the supervision of the HCP to allow continued observation of injection technique and AEs; all other scheduled SC injections should occur outside of the clinic. HCPs will have appropriate monitoring and treatment for hypersensitivity reactions available for use following administration of study drug. Subjects who experience a severe hypersensitivity reaction associated with study drug administration will be discontinued from the study (see Section 7.4).

Subjects and their caregivers will be instructed to inject SC doses into the thigh, abdomen, or upper arm, and to rotate the injection sites. Subjects and their caregivers will be instructed that the upper arm is to be used only when the caregiver administers the SC injection. Details on the training protocol and injection technique will be included in the appropriate Study Manual. For all dosing occurring outside of the clinic, subjects will receive a phone call from study staff within 24 hours prior to every injection for these scheduled doses to administer the PML subjective checklist and enquire about general health status and experience with prior injection. In accordance with the Risk Assessment and Management Plan for PML (RAMP), any positive PML subjective finding must be evaluated via the physician administered PML objective checklist prior to the subject receiving the respective dose (refer to RAMP Site Staff Brochure). Subjects will also receive a phone call from their HCP within 12 hours after the home injection at Weeks 10 and 12 to enquire about health status and experience with injection unless they attended the clinic on these days. AEs reported by the subject will be handled in accordance with Section 10.0 of the protocol.

Subjects who do not participate in the OLE study or are discontinued from the study before Week 6, will enter the Follow-Up Period and complete a final on-study safety assessment at 18 weeks (ie, 5 vedolizumab half-lives) after the last study drug dose.

Additionally, subjects who do not participate in the OLE study or a discontinued before Week 6 will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.

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

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Figure 6.a Schematic of Study Design

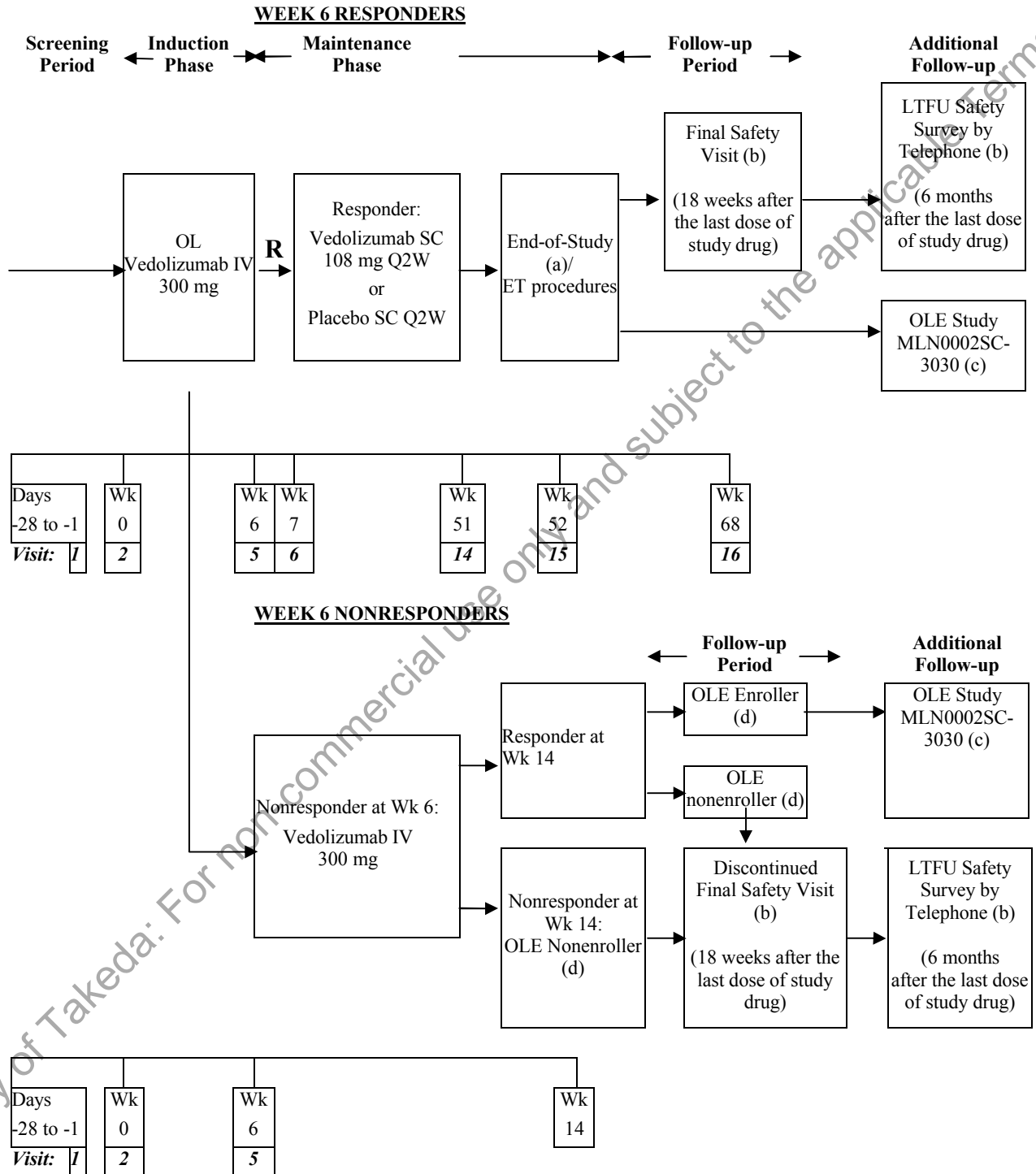


Figure 6.a footnotes on next page.

OL=open-label, R=randomization.

- (a) Maintenance Period: Subjects who ET (Table 7.a) may consent to participate in the OLE study (MLN0002SC-3030) and may enter the OLE study and begin OLE study dosing after End-of-Study Visit procedures have been completed.
- (b) For subjects who do not enroll into the OLE study (MLN0002SC-3030) (including early terminators before Week 6 in the Maintenance Phase)
- (c) First visit of OLE Study MLN0002SC-3030 is within 4 weeks after last dose of study drug for Week 52 completers/ET or 1 week of Week 14 for Week 14 responders.
- (d) Week 14 responders and nonresponders (OLE enroller/nonenroller) will complete the procedures as per the Schedule of Assessments (Appendix A).

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

This phase 3 study is designed to evaluate the efficacy, safety, PK, and immunogenicity of multiple injections of the new presentation, vedolizumab SC, as maintenance therapy in subjects with CD. The proposed vedolizumab SC maintenance dosing regimen (108 mg Q2W) was selected to provide similar exposure to that from the approved IV vedolizumab dosing regimen (300 mg Q8W). Therefore, the safety and efficacy of the vedolizumab SC presentation are expected to be similar to those of vedolizumab IV, outside of expected local administration site events, such as injection-site reactions.

The study design allows for independent assessments of vedolizumab SC efficacy as maintenance therapy in subjects who responded to vedolizumab IV by comparing the active therapy to the placebo group during the Maintenance Phase. It also permits double-blind, placebo-controlled comparisons of safety parameters during the Maintenance Phase. Additional measures will be taken to collect safety parameters beyond the 52-week duration of the trial, where a Final Safety Follow-up Visit will be conducted 18 weeks (>5 half-lives) after the subject's final dose of study drug if they do not enroll in the OLE, and additional safety information will be collected by telephone using a LTFU survey at 6 months after the last study drug dose (for both SC and IV dosing).

The entry criteria ensure that subjects who are appropriate for treatment with biologic agents, as assessed by severity of disease and failure of 1 or more standard therapies (ie, corticosteroids, immunomodulators, or TNF- $\alpha$  antagonists), will be enrolled into the study. Entry criteria will also exclude subjects who might not benefit from drug or who might be at risk for treatment toxicities. Additional measures to ensure the safety of enrolled subjects include protocol mandated criteria for withdrawal from the study of subjects who experience worsening of disease or require rescue medication (ie, any new medication or any increase in dose of a baseline medication required to treat new or unresolved CD symptoms, other than antidiarrheals for control of chronic diarrhea). Thus, subjects who may be treated with placebo (inactive treatment) between Weeks 6 and 52 will be withdrawn from the study if they experience treatment failure (ie, disease worsening after Week 6, need for rescue medications after Week 14), but may be eligible to enroll in the OLE study.

At Week 6, subjects receiving oral corticosteroids who achieve clinical response must begin a corticosteroid tapering regimen as described in Section 7.3.1.1. Subjects are allowed to continue

background therapy such as 5-ASAs or immunomodulators, as indicated in the Permitted Medications and Treatments in Section 7.3.1.

The primary efficacy endpoint of this study is clinical remission, defined as a CDAI score  $\leq 150$  points, at Week 52. To further characterize the clinical efficacy and safety of vedolizumab SC, secondary and additional endpoints include enhanced clinical response at Week 52, corticosteroid-free remission at Week 52, and durable clinical remission.

Disease activity for entry into this study and for efficacy assessments throughout the study will be measured by the CDAI, a standard assessment tool to measure CD disease activity in clinical trials [36], CCI. CDAI includes 3 subjective items (number of liquid stools, abdominal pain and general wellbeing), and 5 objective items (number of extraintestinal complications, use of antidiarrheal drugs, presence of abdominal mass, hematocrit, and ideal/observed body weight ratio). CCI

Exposure-efficacy analyses were conducted using either observed or population model predicted vedolizumab concentrations from the phase 3 vedolizumab IV studies. In both the quartile analysis using the  $C_{\text{trough}}$  and the logistic regression analysis using the population PK model predicted  $C_{\text{av}}$  ( $C_{\text{av}} = \text{AUC}_{\tau} / \tau$ ), there was an apparent exposure-efficacy relationship in subjects with UC for both the Induction and Maintenance Phases, where higher vedolizumab concentrations were associated with higher efficacy. Although the exposure-efficacy relationship demonstrated in UC subjects was not as clear in CD subjects participating in the vedolizumab IV phase 3 studies, the vedolizumab SC dosing regimen selection is applicable to CD subjects based on the following important considerations:

- Vedolizumab targets the same mechanism of action in both the UC and CD indications.
- Vedolizumab IV was effective in inducing and maintaining remission in subjects with moderately to severely active UC or CD who had failed conventional and/or TNF- $\alpha$  antagonist therapy.
- No differences in PK, safety or immunogenicity between the UC or CD subjects were observed in the vedolizumab IV phase 3 studies.

Based on the exposure-efficacy relationship for vedolizumab IV, the vedolizumab SC dosing regimen was selected to provide lower trough concentrations than the vedolizumab IV Q4W regimen and similar exposure to that from the approved vedolizumab IV Q8W regimen (300 mg vedolizumab IV at Weeks 0 and 2, followed by 300 mg Q8W starting from Week 6) during the Maintenance Phase. It is expected that similar exposure to vedolizumab will result in similar efficacy and safety during maintenance, independent of the dosing route or formulation.

In addition to efficacy and safety evaluations, the multiple dose PK and immunogenicity of vedolizumab SC in subjects during the Maintenance Phase will be evaluated in this study. Given the long half-life of vedolizumab (approximately 25 days), blood samples will be collected up to 18 weeks (>5 half-lives) after the last dose to assess the PK of vedolizumab IV followed by vedolizumab SC.

During the Maintenance Phase of this study, vedolizumab SC or placebo SC injections will be administered by the subjects or their caregivers both at clinic visits (Weeks 6, 8, 14, 22, 30, 38, 46, and 50 under HCP supervision) and outside of the clinic. HCPs will train the subjects (and their caregivers) on the adequate technique to prepare and inject study drug during at least at the Week 6 and 8 clinic visits, and will also provide instructions on adequate storage of vedolizumab SC, disposal of used prefilled syringe and needles, hypersensitivity reaction management, and contact information for any questions on vedolizumab SC use. Details on the training protocol and injection technique will be included in the appropriate Study Manual.



### **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 1 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.
- The Data Monitoring Committee recommends the study should be suspended or terminated.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

#### **6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites**

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

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

In the event that the sponsor, an 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.

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## 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 or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject has a diagnosis of CD established at least 3 months prior to screening by clinical and endoscopic evidence, and corroborated by a histopathology report. Cases of CD established at least 6 months prior to screening for which a histopathology report is not available will be considered based on the weight of evidence supporting the diagnosis and excluding other potential diagnoses, and must be discussed with the sponsor on a case-by-case basis prior to entry.
4. The subject is male or female and aged 18 to 80 years, inclusive.
5. 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.
6. 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.

7. The subject has moderately to severely active CD as determined by a CDAI score of 220 to 450 within 7 days prior to the first dose of study drug and 1 of the following:
  - CRP level >2.87 mg/L during the Screening Period OR
  - Ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each >0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous cm of intestine) consistent with CD, within 4 months prior to Screening OR
  - Fecal calprotectin >250 mcg/g stool during the screening period in conjunction with computed tomography enterography, magnetic resonance enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing CD ulcerations

- (aphthae not sufficient), within 4 months prior to screening. (Subjects with evidence of fixed stenosis or small bowel stenosis with prestenotic dilatation should not be included).
8. The subject has CD involvement of the ileum and/or colon, at a minimum.
  9. Subjects with extensive colitis or pancolitis of >8 years duration or left-sided colitis >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial Screening Visit (if not performed in previous 12 months, must be performed during Screening).
  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).
  11. 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, at least one 8-week regimen of oral azathioprine ( $\geq 50$  mg) or 6-mercaptopurine ( $\geq 30$  mg) (Japan only) OR
      - ii. The subject has signs and symptoms of persistently active disease despite a history of at least one 16-week regimen of methotrexate of 25 mg/week OR
      - iii. The subject has a history of intolerance of at least 1 immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, thiopurine S-methyltransferase genetic mutation, infection).
    - Corticosteroids
      - i. The subject has signs and symptoms of persistently active disease despite a history of a least one 4-week induction regimen that included at dose equivalent to prednisone  $\geq 30$  mg daily orally for 2 weeks or intravenously for 1 week, OR
      - ii. The subject has had 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions. In Japan, at least 1 failed attempt to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally or intravenously, OR
      - iii. The subject has a history of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection).
      - iv. The subject had a relapse within 3 months of stopping steroids.

- TNF- $\alpha$  antagonists:
  - i. The subject has signs and symptoms of persistently active disease despite a history of at least 1 induction with:
    - Infliximab: At least 4-week regimen of 5 mg/kg, 2 doses at 2 weeks apart, OR
    - Adalimumab: At least 80 mg on Day 1 and 40 mg on Day 15, OR
    - Certolizumab pegol: At least 400 mg SC at Weeks 0, 2, and 4, OR
  - ii. The subject has recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit OR
  - iii. The subject has a history of intolerance of at least 1 TNF- $\alpha$  antagonist (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection).

## 7.2 Exclusion Criteria

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

### 7.2.1 Gastrointestinal Exclusion Criteria

1. The subject has evidence of abdominal abscess at the initial Screening Visit.
2. The subject has had extensive colonic resection, subtotal or total colectomy.
3. The subject has a history of >3 small bowel resections or diagnosis of short bowel syndrome.
4. The subject has received tube feeding, defined formula diets, or parenteral alimentation within 28 days prior to the administration of the first dose of study drug.
5. The subject has ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
6. The subject has received any of the investigational or approved non-biologic therapies (eg, cyclosporine, tacrolimus, thalidomide, methotrexate, or tofacitinib except for those specifically listed in the protocol Section 7.3.1 Permitted Medications for the Treatment of CD) for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever is longer).
7. The subject has received any investigational or approved biologic or biosimilar agent within 60 days or 5 half-lives of screening (whichever is longer).
8. The subject has used topical (rectal) treatment with 5-ASA or corticosteroid enemas/suppositories within 2 weeks of the administration of the first dose of study drug.
9. The subject currently requires or is anticipated to require surgical intervention for CD during the study.

10. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
11. The subject has a history or evidence of colonic mucosal dysplasia.
12. The subject has a suspected or confirmed diagnosis of ulcerative colitis, indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis.

### 7.2.2 Infectious Disease Exclusion Criteria

13. The subject has evidence of an active infection during the Screening Period.
14. The subject has evidence of, or treatment for, *C. difficile* infection or other intestinal pathogen with 28 days prior to first dose of study drug.
15. The subject has chronic hepatitis B virus (HBV) infection\* or chronic hepatitis C virus (HCV) infection.  
\* HBV immune subjects (ie, being hepatitis B surface antigen [HBsAg] negative and hepatitis B surface antibody [HBsAb] positive) may, however, be included.
16. The subject has active or latent TB as evidenced by the following:
  - i. A positive diagnostic TB test within 30 days prior to screening or during the screening period, defined as:
    1. A positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, (or, A positive T-SPOT TB test [Japan only]),  
OR,
    2. A tuberculin skin test reaction  $\geq 5$  mm.  
Note: if subjects have received BCG vaccine then a QuantiFERON TB Gold test should be performed instead of the tuberculin skin test
  - OR
  - ii. Chest X-ray within 3 months prior to Week 0 which is suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON tests (or, A positive T-SPOT TB test [Japan only]) within 30 days prior to Screening or during the Screening Period.  
Note: subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study.
17. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
18. The subject has received any live vaccinations within 30 days prior to screening.
19. The subject has clinically significant infection (eg, pneumonia, pyelonephritis) within 30 days prior to screening, or ongoing chronic infection.

### 7.2.3 General Exclusion Criteria

20. The subject has had previous exposure to approved or investigational anti-integrin antibodies (eg, natalizumab, efalizumab, etrolizumab, AMG 181), anti-MAdCAM-1 antibodies or rituximab.
21. The subject has had previous exposure to vedolizumab.
22. The subject has had hypersensitivity or allergies to any of the vedolizumab excipients.
23. 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.
24. The subject has had any surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.
25. The subject has any history of malignancy, except for the following: (a) adequately-treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to screening; and (c) 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 remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received and must be discussed with the sponsor on a case-by-case basis prior to screening.
26. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
27. The subject has a positive PML subjective symptom checklist at Screening (or prior to the administration of the first dose of study drug at Week 0).
28. 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 < $3 \times 10^9/L$ .
  - iii. Lymphocyte count < $0.5 \times 10^9/L$ .
  - iv. Platelet count < $100 \times 10^9/L$  or > $1200 \times 10^9/L$ .
  - v. ALT or AST > $3 \times$  the upper limit of normal (ULN).
  - vi. Alkaline phosphatase > $3 \times$  ULN.
  - vii. Serum creatinine > $2 \times$  ULN.
29. Removed in Amendment 03.
30. 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 screening.

31. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
32. The subject or caregiver is unable to attend all the study visits or comply with study procedures.
33. The subject is required to take excluded medications listed in Section 7.3.
34. The subject is unwilling or unable to self-inject, or does not have a caregiver (defined as a legal adult) to inject the study medication.
35. Female subjects who are lactating or have a positive serum pregnancy test during the Screening Period or a positive urine pregnancy test at Week 0, prior to study drug administration.
36. If female, the subject is intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
37. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
38. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

### 7.3 Excluded Medications and Treatments

The following medications are excluded from use during the study (from informed consent to Week 68):

- Any treatment for CD other than those listed in Section 7.3.1 (either approved or investigational).
- All live vaccines from 30 days prior to screening to 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).
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use. (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc. and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted.)
- Leukocytapheresis (white blood apheresis) or granulocytapheresis (Japan only).
- Enteral nutrients (>900 kcal/day) (Japan only).
- 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 subject may be receiving a therapeutic dose of the following drugs:
  - Oral 5-ASA compounds provided that the dose has been stable for the 2 weeks immediately prior to first dose of study drug. The dose of these medications should remain stable throughout the study.
  - Oral corticosteroid therapy (prednisone at a stable dose  $\leq 30$  mg/day, budesonide at a stable dose  $\leq 9$  mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to first dose of study drug if corticosteroids have just been initiated, or for the 2 weeks immediately prior to first dose of study drug if corticosteroids are being tapered. Corticosteroid doses should remain stable until the subject meets the criteria for initiating a corticosteroid tapering regimen (see Section 7.3.1.1).
  - Probiotics (eg, Culturelle, *Saccharomyces boulardii*) provided that the dose has been stable for the 2 weeks immediately prior to first dose of study drug. The dose for these medications should remain stable throughout the study.
  - Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea. Stable doses are encouraged.
  - Azathioprine, 6-mercaptopurine, or methotrexate provided that the dose has been stable for the 8 weeks immediately prior to first dose of study drug. Dose(s) should remain stable unless the medication is discontinued due to a toxicity related to the medication. Even if the toxicity resolved, azathioprine, 6-mercaptopurine, or methotrexate will not be restarted.
  - Antibiotics used for the treatment of CD (eg, ciprofloxacin, metronidazole) provided that the dose has been stable for the 2 weeks immediately prior to first dose of study drug. The dose of these medications should remain stable throughout the study.
- For immunosuppressives, oral 5-ASAs, probiotics and antibiotics for CD, dose reduction or discontinuation will be allowed per label only due to adverse reactions. For oral corticosteroid, as per the tapering schedule (see Section 7.3.1.1).
- Enteral nutrients ( $\leq 900$  kcal/day), stable for at least 3 weeks prior to enrollment. The dosage may be modified after Week 6; however it should preferably remain the stable dose and not exceed the initial dosage (Japan only).
- **Need for rescue medication**: In this study, any new medication or any increase in dose of a baseline medication required to treat new or unresolved CD symptoms (other than antidiarrheals for control of chronic diarrhea) is considered a rescue medication. An increase in corticosteroid dose back to baseline for subjects undergoing corticosteroid tapering within the guidelines presented in Section 7.3.1.1 is not considered rescue medication. Administration of rescue medications, approved or investigational, constitutes treatment failure. Rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety.

### 7.3.1.1 Oral Corticosteroid Dosing and Tapering

At Week 6, subjects receiving oral corticosteroids who achieved clinical response will begin a corticosteroid tapering regimen. The 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 dose 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.
- For budesonide, the dose should be tapered at a rate of 3 mg every 3 weeks.

For subjects who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may be increased up to the original dose at the start of induction therapy (should not exceed baseline dose). In such cases, the tapering regimen above must be reinitiated within 2 weeks. Subjects who require consistent higher doses should be withdrawn from the study according to Section 7.4.

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 9.1.22.

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.

- 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, 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. Three attempts to contact the subject must be documented (ie, 2 attempts by phone and 1 attempt by registered letter).
- 4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

- 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 subject should be discontinued from the study if the following criteria apply:
  - Treatment failure during the Maintenance Phase, defined as disease worsening (as defined in Section 3.5), need for rescue medications (as defined in Section 7.3.1), or need for surgical intervention for treatment of CD.
- 8. Leukopenia or Lymphopenia: WBC and lymphocyte counts will be monitored for all subjects. Azathioprine, 6-mercaptopurine, or methotrexate, if applicable, should be discontinued and the dose of study drug held for an absolute lymphocyte count  $<0.5 \times 10^9/L$  at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of study drug can be administered only if the absolute lymphocyte count is  $\geq 0.5 \times 10^9/L$ . If the absolute lymphocyte count remains  $<0.5 \times 10^9/L$ , study drug should be discontinued and the subject withdrawn from the study.

- 9. Other.

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

Subjects who discontinue due to lack of efficacy are permitted to enroll in the OLE study (MLN0002SC-3030) according to the criteria in Table 7.a.

**Table 7.a Eligibility for Study MLN0002SC-3030 Based on Reason for Withdrawal**

Reason for Withdrawal	Time Point		
	Prior to Week 6	Weeks 6-14	Beyond Week 14
Disease worsening (a)	Not applicable	Eligible	Eligible
Requires rescue medication, but does not meet criteria for disease worsening	Not applicable	Not eligible	Eligible
AE related to study drug leading to discontinuation of study drug	Not eligible	Not eligible	Not eligible
Requires surgical intervention for CD	Not eligible	Not eligible	Not eligible

(a) See Section 3.5 for study definitions.

### 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 (if applicable), Final Safety Visit, and LTFU. Discontinued or withdrawn subjects will not be replaced.

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## 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

### 8.1 Study Medication and Materials

#### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

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

##### 8.1.1.1 *Vedolizumab for Injection, for Intravenous Use (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 for injection. 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.

There is no placebo IV for this study.

Additional reference information and administration instructions can be found in the Pharmacy Manual.

##### 8.1.1.2 *Vedolizumab Injection, for Subcutaneous Use (Vedolizumab SC)*

The study sites will be supplied with the following medication in a blinded manner: vedolizumab SC 108 mg/0.68 mL or placebo in a pre-filled syringe. The study medication is a liquid presentation provided in pre-filled syringe with backstop and plunger rod assembled together. Each syringe will be packaged in folding box or carton.

The subcutaneous placebo is a liquid solution supplied at 0.68 mL in pre-filled syringes for SC injection with similar formulation composition as the vedolizumab SC solution, and administered via SC injection.

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.

#### 8.1.1.3 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following:

- Vedolizumab for Injection, for Intravenous Use (vedolizumab IV).
- Vedolizumab Injection, for Subcutaneous Use (vedolizumab SC)/vedolizumab SC placebo.

#### 8.1.1.4 Other Protocol-Specified Materials

The following supplies will also be required for study drug administration and are to be provided by the clinical study center unless otherwise indicated:

- Bottled sterile water for injection (for study drug reconstitution).
- 250 mL 0.9% sodium chloride for injection in polyvinyl chloride (PVC) IV bag(s) or 250 mL 0.9% sodium chloride in alternative IV bags or bottles listed in the Pharmacy Manual. (100 mL in Japan).
- PVC infusion line or alternative infusion line listed in the Pharmacy Manual.
- Alcohol swabs.
- Needle sharps container (provided by sponsor).

### 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 and vedolizumab SC 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**

Treatment Group	Dose	Treatment Description	
All Subjects	Vedolizumab IV 300 mg	Open-label	Weeks 0 and 2
A (Week 6 Nonresponders)	Vedolizumab IV 300 mg	Open-label	Week 6
B	Vedolizumab SC 108 mg	Blinded	Weeks 6-50 (Q2W)
C	Vedolizumab SC Placebo	Blinded	Weeks 6-50 (Q2W)

#### 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, Adverse Events (AEs), and Product Complaints (PC).

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

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

#### 8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive treatment according to the schedule allocated to each study site.

The investigator or investigator's designee will access the interactive web response system (IWRS) at screening to register a subject and obtain a subject identification number to identify the subject throughout the study. The investigator or the investigator's designee will use the 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 IWRS as well as at subsequent visits. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IWRS. Refer to the appropriate study manual provided separately for additional information.

For IV infusion, subjects will receive a 300 mg dose of vedolizumab IV infusion over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on study observations. Vedolizumab IV should be administered by a HCP prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion 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.

For SC injection, the recommended sites are the abdomen (except for the 2-inch area around the navel), the outer area of the upper arms, or the front of the thighs. The arm injection site should be used only by caregivers administering the injection. The injection site should be changed for consecutive injections. Each new injection should be given at least 1 inch from a site used before.

During clinic visits, SC injections should be administered by the subject (or caregiver) under the supervision of a HCP prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate

use. Subjects should be observed during the administration and for 1 hour following completion of the administration.

Study medication storage, disposal and directions for use for the subject self-injections will be described in information provided to the subject.

For further dispensing information, please refer to the pharmacy and/or appropriate study manual.

### 8.3 Randomization Code Creation and Storage

After receiving open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2, subjects will be assessed for clinical response (defined as a  $\geq 70$  point decrease in CDAI score from Baseline [Week 0]) at Week 6). Subjects with clinical response at Week 6 will be randomized at a 2:1 ratio to receive blinded injections of vedolizumab SC 108 mg or placebo SC Q2W, beginning at Week 6 through Week 50.

Randomization will be stratified by:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF- $\alpha$  antagonist failure/exposed or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

Randomization personnel of the sponsor or designee will generate the randomization schedule prior to the start of the study. An IWRS system will be used for subject randomization. All randomization information will be stored in a secured area, accessible only by authorized personnel.

### 8.4 Investigational Drug Blind Maintenance and Unblinding

The investigational drug blind will be maintained using the IWRS. In addition, in order to maintain the blind, all study site personnel will be blinded to the treatment assignments for the duration of the study.

The investigational drug blind may be broken by the investigator if information concerning the investigational drug is essential for the medical treatment of the subject. The medical monitor must be informed of the unblinding at the earliest possible opportunity. In nonurgent cases, the medical monitor must be contacted before the subject is unblinded.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IWRS. The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and eCRF as appropriate.

## 8.5 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee and delegated pharmacy staff, 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 vials and vedolizumab SC/placebo SC pre-filled syringes], the appropriate person must maintain respective 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.

Records of the subject number, the date study drug was dispensed, and the study drug/cohort assignment will be maintained by the pharmacist.

Upon receipt of sponsor-supplied drug, the appropriate pharmacist 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, they should acknowledge the receipt of the shipment (by signing the bottom half of the packing list and faxing per instructions provided on the form/ or by recording in IWRS). If there are any discrepancies between the packing list and 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 (pharmacy file).

The pharmacist must maintain 100% accountability for all sponsor-supplied drugs received and dispensed. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the (drug lot/medication ID/job number) used to prepare each dose.
- Verifying that all containers used/assigned 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 IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The pharmacist 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, date and amount returned to the site by the subject, and the initials, seal, or signature of the person dispensing the drug. The

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

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

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



## 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 by IWRS to each subject at the time of screening; this subject number will be used throughout the study.

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#### 9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age or date of birth (depending on local regulations), sex, Hispanic ethnicity (as applicable, United States only), 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.

### 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; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

### 9.1.4 Weight and 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 (sitting), and pulse (bpm). On dosing days, vital signs are taken predose.

### 9.1.6 Primary Efficacy Measurement

Primary efficacy assessments during the Maintenance Phase will be based on CDAI scores. During screening, subjects will be instructed on how to appropriately complete the diary. The symptoms of CD must be recorded throughout the study, including the Screening Period. A validated electronic system will be used for collection of the patient diary.

On all dosing visits CDAI components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components.

#### 9.1.6.1 Diary Completion and Review

Diary entries will be made daily by subjects from screening to end of study, and will be used for CDAI calculation. At 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 a validated electronic system. At each visit, including during screening, the CDAI score must be calculated prior to dosing by the CCI, accessed by the investigator or designee based on daily diaries, laboratory assessments, and clinical examination and recorded in the subject's source documents.

The CDAI score evaluated during screening will be used to determine eligibility, using subject diary entries within 10 days prior to Week 0. At a minimum, 7 days of diary data from the last 10 days prior to Week 0 will be required for the calculation of the score. Subjects will be required to complete diary entries for at least 14 days prior to Week 0. CCI

The Week 6 total CDAI score will be used to determine whether the subject has achieved clinical response at Week 6 (a  $\geq 70$ -point decrease in CDAI score from baseline [Week 0]), and will determine eligibility for randomization in the Maintenance Phase.

Entries should be reviewed and monitored by the study staff (see the appropriate Study Manual).

#### **9.1.7 Documentation of Concomitant Medications**

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Medications used specifically for premedication purposes will be collected separately 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, 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 24 mL, and the approximate total volume of blood for the study is 260 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.

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

**Table 9.a Clinical Laboratory Tests**

Hematology	Serum Chemistry	Urinalysis
RBC	ALT	Bilirubin
WBC w/ differential	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit	Amylase	Ketones
Platelets	Lipase	Leukocyte esterase
PT/INR	AST	Nitrite
	Total and direct bilirubin	pH
	Total protein	Protein
	Creatinine	Specific Gravity
	Blood urea nitrogen	Microscopic (to be obtained in the event of positive leukocyte esterase or blood, will include WBCs, RBCs, and cast[s])
	Creatine kinase	
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Bicarbonate	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	
<b>Other:</b>		
HIV		Beta hCG and Urine Pregnancy hCG
Hepatitis panel, including HBsAg, HBsAb, and anti-HCV (a)		(female subjects of childbearing potential)
CRP		FSH (b)
Fecal Calprotectin		<i>C. difficile</i>
CCI		
CCI		
QuantiFERON for TB		
PK		

CRP= C-reactive Protein, FSH=follicle-stimulating hormone, GGT=  $\gamma$ -Glutamyl transferase, hCG=human chorionic gonadotropin, HBsAb=antibody to hepatitis B surface antigen, PT=prothrombin time, RBC=red blood cells.  
 (a) HBV immune subjects (ie, being HBsAg negative and HBsAb positive) may, however, be included.  
 (b) FSH level will be obtained for female subjects at Screening if they are postmenopausal by history (ie, last regular menstrual cycle >1 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.

Central laboratories will perform laboratory tests for hematology, serum chemistries, and urinalysis as well as specialty testing outlined above. The results of safety laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Refer to the schedule of events for timing of all assessments.

If subjects experience ALT or AST  $>3 \times \text{ULN}$ , follow-up laboratory tests should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

(Please refer to Section 7.4 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST  $>3 \times \text{ULN}$  in conjunction with total bilirubin  $>2 \times \text{ULN}$ .)

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

#### 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  $>40$  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 will be:

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

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, subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures ([Appendix A](#)).

All female subjects of child bearing potential will have a serum pregnancy test during screening and at Week 52 (or ET Visit) and Week 68 (or Final Safety Visit). A urine pregnancy test will be completed for all females of child bearing potential on a 4-weekly basis prior to administration of study drug.

### 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 and returned to the study site. In addition, any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose, should also be recorded following authorization from the subject's partner.

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

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject, 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 was participating in a clinical study at the time the subject/female partner of the subject 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.

Any findings from ECGs collected after study drug administration at Week 0 will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

Subjects will be supine and will have rested for 5 or more minutes before any ECG is recorded. Tracings will include subject number and initials and the date and time of recording.

#### 9.1.13 CCI

[Redacted text block]

#### 9.1.14 CCI

[Redacted text block]

#### 9.1.15 CCI

[Redacted text block]

CCI



#### **9.1.16 Tuberculosis Screening**

All subjects will complete TB screening to determine eligibility. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section [7.2.2](#).



9.1.17 CCI [REDACTED]

CCI [REDACTED]

### 9.1.18 Stool Sample

A stool sample will be obtained for culture, ova and parasite evaluation, and *C. difficile* assay. A sample will be collected and cultured during screening and at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.

### 9.1.19 PML Checklist

Staff will administer the subjective PML checklist during screening to exclude subjects with positive responses from enrolling into the study. The PML subjective checklist will be administered in person prior to dosing at visits occurring in the clinic. The PML subjective checklist will be administered over the phone prior to dosing when the subject is self-injecting outside of the clinic.

Any subjects reporting signs or symptoms of PML will be told to withhold the respective dosing and will undergo physician administered objective testing and may be referred to a neurologist for a full evaluation, as described in the RAMP Algorithm referenced in Section 11.2.1. The symptoms from a positive PML checklist will be recorded as an AE in the eCRF. Additional information and tools for the RAMP can be found in the appropriate Study Manual.

### 9.1.20 Patient Reported Outcomes Instruments

Subjects will complete the IBDQ and EQ-5D health related quality-of-life (HRQOL) questionnaires at the time points specified in the schedule of events. CCI [REDACTED]

#### 9.1.20.1 Inflammatory Bowel Disease Questionnaire

The IBDQ is a valid and reliable [37] instrument used to assess quality of life (QOL) in adult subjects with IBD. It includes 32 questions on 4 domains of HRQOL: Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Subjects are asked to recall symptoms and QOL from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher QOL). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224.

#### 9.1.20.2 EQ-5D Questionnaire

The EQ-5D questionnaire, developed by the 'EuroQol Research Foundation' is a simple, valid, and reliable [38] instrument used to measure general health-related QOL in subjects and includes 5 domain items - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Subjects 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.

9.1.20.3 CCI [Redacted]

CCI [Redacted]

9.1.21 CCI [Redacted]

CCI [Redacted]

**9.1.22 Documentation of Screen Failure**

Investigators must account for all subjects who sign informed consent.

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

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

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.

- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused. Re-screening of subjects will be assessed by the Medical Monitor on a case by case basis.

### 9.1.23 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria at Week 0 are eligible for enrolment into the Induction Phase.

At Week 6 subjects will be assessed for eligibility for randomization into the Maintenance Phase.

If the subject is found to be not eligible for the study, 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 reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

## 9.3 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 9.1.22 for procedures for documenting screening failures.

Procedures to be completed at screening can be found in the schedule of events ([Appendix A](#)).

### 9.3.2 Enrollment/Randomization

Enrollment will take place at Week 0. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria, the subject should be enrolled using the 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 9.1.22.

Eligible subjects will receive open-label infusions of vedolizumab IV 300 mg at Weeks 0 and 2, and will be assessed for clinical response (defined as a  $\geq 70$  point decrease in CDAI score from baseline [Week 0] at Week 6). Subjects with clinical response at Week 6 will be randomized at a 2:1 ratio to receive blinded injections of vedolizumab SC 108 mg or placebo SC Q2W, beginning at Week 6 through Week 50.

Randomization will be stratified by:

- Concomitant use of oral corticosteroids.
- Clinical remission status at Week 6.
- Previous TNF- $\alpha$  antagonist failure/exposed or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

#### 9.3.2.1 Nonresponders

Subjects who are nonresponders at Week 6 and hence are not randomized into the Maintenance Period of the study will receive a third vedolizumab IV infusion at Week 6. Subjects who achieve a clinical response (by CDAI score) at Week 14 are eligible to enroll in the OLE study. Subjects who respond at Week 14 but do not enroll into the OLE study, and subjects who do not respond at Week 14 will be discontinued.

#### 9.3.3 Final Visit or ET

The Final Visit will be performed on Week 52 or at ET for all subjects who enter the Maintenance Phase.

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

Subjects who complete the study will be offered entry into the OLE study after completion of the Week 52/ET assessment. Week 0 of the OLE study should occur within 4 weeks of the last dose of study drug for Week 52 completers/ET.

Subjects at Week 14 who are responders and are eligible to participate in the OLE will not complete an ET visit but complete procedures as per the Schedule of Study Procedures ([Appendix A](#)). For Week 14 responders, subjects should receive their first OLE vedolizumab SC dose as close to Week 14 as possible (preferably within Week 14  $\pm 3$  days). If this window is too challenging for the sites, dosing within week 14  $\pm 7$  days is acceptable from a PK perspective (ie, maintaining trough concentration at or above 10  $\mu\text{g/mL}$ ).

Subjects who are discontinued due to disease worsening (after Week 6) during the Maintenance Period will be offered entry into the OLE study.

From Week 14 onwards, subjects in the Maintenance Phase who are withdrawn from the study due to need for rescue medications, despite not meeting the criteria for disease worsening, will be offered entry into the OLE study. Rescue medications are defined as any new medication or any

increase in dose of a baseline medication required to treat new or unresolved CD symptoms (other than antidiarrheals for control of chronic diarrhea).

Subjects who are discontinued due to AEs related to study drug that lead to discontinuation or require a surgical intervention for their CD will not be eligible to enroll into the OLE study.

#### 9.3.4 Final Safety Follow-up Visit

For those subjects not entering the OLE study or are discontinued, a Final Safety Follow-up Visit will be performed 18 weeks after the last dose of study drug. Assessments will be completed per the schedule of events Week 68 Visit.

#### 9.3.5 Post Study 6-month Long-Term Follow-Up Survey

Upon completion of (including OLE nonenrollers from Week 14) or ET from the study, all subjects not entering the OLE study will be required to participate by telephone in a LTFU safety survey 6 months after the last dose of study drug (from the last dose received).

#### 9.3.6 Unscheduled Visits Due to Disease Exacerbation

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

- Physical examination.
- Vital signs assessment.
- Diary review.
- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Clinical chemistry and hematology, as indicated.
- Partial or complete CDAI.
- PK sample collection
- CCI
- Stool sample for fecal calprotectin, if indicated.
- *C. difficile*, if indicated.

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.

### 9.3.7 Poststudy Care

Following study end, subjects who meet the relevant eligibility criteria will be provided an opportunity to continue receiving study drug by participating in the OLE study MLN0002SC-3030. Otherwise, study drug will not be available upon completion of the subject's participation in the study and the subject should be returned to the care of a physician and standard therapies as required.

### 9.4 Biological Sample Retention and Destruction

In this study, specimens will be collected as described. The samples will be sent to a central laboratory that processes the samples 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.

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.

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.

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## 10.0 PRETREATMENT EVENTS (PTE) ADVERSE EVENTS (AE) AND PRODUCT COMPLAINTS (PC)

### 10.1 Definitions

#### 10.1.1 PTEs

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

#### 10.1.2 AEs

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

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

In addition, drug-device AEs related to quality or malfunction will be collected.

#### 10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the

investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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



Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

#### 10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
  - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. 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 respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product Neuroleptic malignant syndrome / malignant hyperthermia Spontaneous abortion / stillbirth and fetal death

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

### 10.1.5 Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda. Refer to Section 10.2.1.4 for information for special interest AE reporting.

### 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 a reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

### 10.1.9 Start Date

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

### 10.1.10 Stop Date

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

### 10.1.11 Frequency

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

### 10.1.12 Action Concerning Study Medication

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

### 10.1.13 Outcome

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

### 10.1.14 Product Complaints

A PC is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product and/or device (eg, prefilled syringe).

An investigator who is made aware of or identifies a potential PC should immediately report the event to Takeda in accordance with the contact list provided to the site. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from a Takeda representative. Refer to the appropriate study manual provided separately for additional information (depending on local regulations).

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

#### 10.2.1.1 PTE and AE Collection Period

Start of AE collection: AEs must be collected from start of study medication administration.

End of AE collection: AEs must be collected for 18 weeks following the last dose of study medication.

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication or until

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

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

#### *10.2.1.2 PTE and AE Reporting*

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

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

1. Event term.
2. Start and stop date (and time, if deemed directly related to the study drug administration).
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 patient-reported outcomes measures will be used in this study (eg, IBDQ, EQ5D, CCI). 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 subject 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*

CD is associated with certain characteristic signs and symptoms, including diarrhea 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 are considered medically anticipated clinical events for the condition under study and will not be collected as AEs. These characteristics of disease activity will be regularly captured in the CDAI score and will be reviewed by the Data Safety Monitoring Board (DSMB).

Exacerbations of disease activity (eg, increase in the daily amount of abdominal pain beyond the subject's normal fluctuation, new signs or 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 an SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

#### **Hypersensitivity Reactions (Including Injection Site 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 IV should be administered by a HCP prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measure should be available for immediate use. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

During clinic visits, subjects should be observed during the SC administration and for 1 hour following completion of the administration. Vedolizumab SC should be administered by the subject or caregiver in the presence of a HCP prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measure should be available for immediate use.

Subjects and caregivers will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injections site pain, redness and/or swelling, etc. that may represent an administration-related reaction (ie, injection-site reaction or infusion-related reaction) to study medication. Subjects will be asked to report administration-related AEs to the sites immediately as they are experienced or after having received appropriate medical care. Appropriate treatment and follow-up will be determined by the investigator. If signs or symptoms of an administration-related

reaction are observed during the administration of study medication, it should be immediately discontinued and the subject treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication and investigator supervision) at the discretion of the investigator. Subjects with a severe or serious administration-related reaction (eg, shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs, severe injection site reactions) must be withdrawn from the study (see the appropriate Study Manual).

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

### **Serious Infections**

Subjects will be monitored for signs and symptoms of infection and for lymphopenia during the study. Subjects with signs and symptoms suggestive of infections, including GI infections, will be treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Withholding or terminating study drug administration may be considered as described in Section 7.4.

### **Malignancy**

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

### **Other**

Other special interest AEs include liver injury and PML, which are discussed in Sections 10.2.3 and 11.2.1 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 4.1.

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.

\*Note: For Japanese sites, the investigator should report the detailed paper SAE report provided by sponsor or by the institution without delay after notification of initial information. Additional detailed follow-up data surrounding the serious adverse event that becomes available following the initial report should be communicated through the same channels as outlined above.

### 10.2.3 Reporting of Abnormal Liver Function Tests

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

If a subject is noted to have ALT or AST  $>3 \times \text{ULN}$  and total bilirubin  $>2 \times \text{ULN}$  for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.9 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE Form (as per Section 10.2.2).

### 10.3 Follow-up of SAEs

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

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, 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

### 11.1 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) independent from the sponsor will be established to review unblinded safety data from this study on a regular basis and to make appropriate recommendations regarding the safe conduct of the study.

A detailed charter will outline the activities and scope of the DSMB (eg, type of data reviewed, frequency of meetings and location of meetings).

### 11.2 Adjudication Committee

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

#### 11.2.1 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 CNS. PML is caused by the JCV and typically only occurs in patients who are immunocompromised [40,41]. 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 [42,43]. In contrast, vedolizumab binds to the  $\alpha_4\beta_7$  integrin only [29] 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 appropriate 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 respective dose of study drug will be withheld 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 appropriate Study Manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Subjects will receive training and educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

## 12.0 DATA HANDLING AND RECORD KEEPING

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

### 12.1 Electronic CRFs

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.

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

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

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

1. The following procedure is applied for the countries except for Japan.

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

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

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

2. The following procedure is applied for Japanese site only.

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

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

## 13.0 STATISTICAL METHODS

### 13.1 Statistical and Analytical Plans

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

A blinded data review meeting will be conducted prior to unblinding of subjects' treatment assignment and database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

#### 13.1.1 Analysis Sets

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

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

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

The PK evaluable population is defined as all subjects who receive at least 1 dose of study drug and have sufficient blood sampling to allow for PK evaluation.

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

Baseline and demographic information will be listed and summarized by treatment group and overall. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

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 statistical testing will be performed at 2-sided 0.05 level of significance. To control the overall Type I error rate for the primary and secondary endpoints, the statistical inference for the first secondary endpoint of enhanced clinical response will only be performed if the primary endpoint, proportion of subjects with clinical remission at Week 52, is statistically significant. The second

secondary endpoint of corticosteroid-free clinical remission will only be tested if the first secondary endpoint is statistically significant. All dichotomous efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel tests for risk differences, stratified by randomization stratum. All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis. Multiplicity will not be adjusted across additional endpoints.

#### 13.1.4 Resource Utilization and PRO

All statistical testing will be performed at 2-sided 0.05 level of significance. To control the overall Type I error rate for the comparison between vedolizumab SC and placebo groups, a hierarchy approach will be applied to the PRO endpoints if the primary endpoint is significant.

The order of testing of PRO endpoints in Section 5.2.3 will be finalized in the SAP before database lock.

Changes from Baseline to Week 52 in IBDQ, EQ-5D scores and CCI components will be analyzed in an Analysis of Covariance model with treatment as a factor and baseline score as a covariate. Changes from Week 6 to Week 52 will be analyzed in a similar fashion.

#### 13.1.5 CCI

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#### 13.1.6 Other Analysis

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### 13.1.7 Safety Analysis

Safety analysis will be performed using the Safety Analysis Set. No statistical inference will be made for safety analyses.

The number and percentage of subjects with TEAEs (defined as any AEs, regardless of relationship to study drug), AESIs (ie, serious infections, including opportunistic infection such as PML, malignancies, liver injury, infusion reactions, injection site reactions), and SAEs which occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug in subjects who do not enroll in OLE study or up to the first dose of the OLE study in those who do, will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related adverse events overall and by severity. In addition to incident rates, exposure adjusted AE rates will be summarized as well.

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

Additional summaries of TEAEs will be provided that only include TEAEs that occur in the Maintenance Phase between the Week 6 dose and 18 weeks after the last dose date of the study drug, or up to the first dose of the OLE study, whichever comes first.

Data from the LTFU survey will be summarized descriptively.

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

### 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.



### 13.3 Determination of Sample Size

Assuming a clinical remission rate of 38% for vedolizumab and 22% for placebo at Week 52, a sample size of 258 subjects in the vedolizumab group and 129 subjects in the placebo group will provide 90% power at 2-sided 0.05 level of significance. To ensure a randomized sample size of 387 subjects, assuming 47% of the subjects entering induction will achieve clinical response at Week 6, approximately 824 subjects will need to be enrolled into the study.

## 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.

The procedure below applies to Japanese sites only.

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained. The investigator should document all protocol deviations.

### 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 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.

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

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

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

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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 Americas investigators), country, and recruiting status will be registered and available for public viewing.

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

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

#### **15.4.3 Clinical Trial Results Disclosure**

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

#### **15.5 Insurance and Compensation for Injury**

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

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**Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders**

Study Procedure	Screening	Induction Open Label Treatment Period		Induction Observation		Week 6 Nonresponders Open Label Treatment Period				
		Days -28 to -1	Week 0 (a) Day 1	Week 2 Day 15 (±2 days)	Week 6a (b) Day 43 (-5 days)	Week 6b (b) Day 43 (+3 days)	Week 6b Day 43 (+3 days)	Pre-Week 14 Day 92 (+4 days)	Week 14 (t) Day 99 (±3 days)	
									OLE Nonenroller	OLE Enroller
Clinic Visit Number	1	2	3	4	5	NR5	PW14	NR6	NR6	
Informed consent	X									
<b>CCI</b>										
Demographics	X									
Tobacco use	X									
Medical and CD history	X									
Prior therapies for CD	X									
Physical examination (c)	X	X	X			X		X	X	
Vital signs (d)	X	X	X			X		X	X	
PML checklist (e)	X	X	X			X		X	X	
PML wallet card	X									
Diary instruction	X									
Diary review (f)		X	X			X		X	X	
Concomitant medications and procedures (g)	X	X	X			X		X	X	
<b>CCI</b>										
12-lead ECG	X									
TB screening (i)	X									
Vedolizumab IV OL Dosing (j)		X	X			X				

Footnotes are on last table page.

**Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders (continued)**

Study Procedure	Screening	Induction Open Label Treatment Period		Induction Observation		Week 6 Nonresponders Open Label Treatment Period				
		Days -28 to -1	Week 0 (a) Day 1	Week 2 Day 15 (±2 days)	Week 6a (b) Day 43 (-5 days)	Week 6b (b) Day 43 (+3 days)	Week 6b Day 43 (+3 days) NR5	Pre-Week 14 Day 92 (+4 days) PW14	Week 14 (t) Day 99 (±3 days)	
									OLE Nonenroller NR6	OLE Enroller NR6
<b>Clinic Visit Number</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>					
Randomization					X					
Assess eligibility for OLE									X	
CDAI (k)		X (k)	X		X (k)	X(k)		X (k)	X (k)	
PRO (IBDQ; EQ-5D)		X			X	X			X	
<b>CCI</b>										
PTE/AE assessment (l)	X	X	X	X	X	X		X	X	
SAE assessment (m)	X	X	X	X	X	X		X	X	
<b>Sample collection for:</b>										
Serum pregnancy test	X						X			
Urine pregnancy test (n)		X	X		X	X		X	X	
HBV, HCV, HIV screen	X									
FSH (o)	X									
Clinical chemistry	X	X	X		X	X	X			
Hematology	X (k)	X	X	X (k)	X	X	X (k)			
Coagulation	X									
Urinalysis	X	X			X	X	X			
PK assessment (p)		X			X	X	X	X		
<b>CCI</b>										
Fecal calprotectin (q)	X				X	X	X			
CRP	X	X			X	X	X			
<i>C. difficile</i> stool sample (r)	X									
<b>CCI</b>										

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Study Procedure	Screening	Induction Open Label Treatment Period		Induction Observation		Week 6 Nonresponders Open Label Treatment Period				
		Days -28 to -1	Week 0 (a) Day 1	Week 2 Day 15 (±2 days)	Week 6a (b) Day 43 (-5 days)	Week 6b (b) Day 43 (+3 days)	Week 6b Day 43 (+3 days)	Pre-Week 14 Day 92 (+4 days)	Week 14 (t) Day 99 (±3 days)	
									OLE Nonenroller	OLE Enroller
Clinic Visit Number	1	2	3	4	5	NR5	PW14	NR6	NR6	

Footnotes are on last table page.

Footnotes:

Day=day after the first dose. CCI HBV=hepatitis B virus, HCV=hepatitis C virus, NR=non-responders, OL=open-label, PML=progressive multifocal leukoencephalopathy, CCI.

(a) All Baseline (Week 0) assessments will be done pre-dose.

(b) Week 6a visit should be performed between Day 38 and 43 (inclusive) and Week 6b visit should be performed between Days 43 and 46 (inclusive). The Week 6a and 6b visits should not be performed on the same day.

(c) Physical examination: Clinically significant findings will be recorded as concurrent conditions if they started prior to signing the informed consent, or as PTEs if they started after signing the informed consent and as AEs if they started after the first dose of study drug.

(d) Vital signs: Height (cm) and weight (kg; without shoes) will be measured during screening. Weight and vital signs will also be measured on dosing days prior to dosing.

(e) PML checklist: will be administered prior to each dosing event. The PML subjective checklist will be administered in person at dosing occurring in the clinic during scheduled visits. The PML subjective checklist will be administered over the phone when the subject is injecting outside of the clinic.

(f) Diary review: will be administered prior to each dosing event either in person at dosing occurring in the clinic during scheduled visits or over the phone when the subject is injecting outside of the clinic.

(g) Concomitant medications and procedures: Monitoring of concomitant medications and concomitant procedures will begin at signing of the informed consent.

(h) CCI

(i) TB screening: To be performed prior to dosing.

(j) Week 0 and 2 dosing will be done with vedolizumab IV; from randomization at Week 6B onwards dosing will be done with vedolizumab SC. WK6 Nonresponders (NR) will receive a 3<sup>rd</sup> infusion with open-label vedolizumab IV and be assessed for response at WK14. Responders at Week 14 will be eligible for the OLE study, Week 14 Responders that do not enter the OLE study and Nonresponders at Week 14 will complete Visit NR6 and discontinue from the study.

(k) CDAI: CDAI score components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components. Hematocrit level from central laboratory results will be used for calculation of the CDAI score.

The components of the CDAI score to determine eligibility at Week 0 must be available within 7 days prior to receiving the first dose of study drug (at a minimum, 7 days of diary data from the last 10 days prior to Week 0 will be required for the calculation of the score and the hematocrit level from Screening. Subjects will be required to complete diary entries for at least 14 days prior to Week 0). For Randomization at Week 6b, the sample taken for the hematocrit at Week 6a will be used to calculate the CDAI score. For Week 14, the sample taken for hematocrit at pre-Week 14 will be used to calculate the CDAI score.

(l) PTEs will be captured immediately following the signing of the informed consent at Screening, up until the first dose of study drug. Collection of AEs, to include concomitant

medications, will begin following first dose of study drug and will continue through Week 68/Final Safety Visit. To be performed in person at dosing occurring in the clinic during scheduled visit. To be performed over the phone at dosing occurring outside of the clinic.

(m) Collection of all SAEs will begin once the informed consent is signed and will continue through Week 68/ Final Safety Visit. To be performed in person at dosing occurring in the clinic during scheduled visit.

(n) A urine pregnancy test will be completed for all female subjects of child bearing potential on a 4-weekly basis prior to administration of study drug.

(o) Follicle-stimulating hormone (FSH) level will be obtained for female subjects at Screening if they are postmenopausal by history (ie, last regular menstrual cycle >1 years) and not surgically sterile. The FSH result must be >40 IU/L for the subject to be permitted not to use adequate contraception.

(p) All PK CCI samples will be obtained at predose (within 30 minutes prior to dosing).

(q) Fecal calprotectin stool sample should be collected from the first bowel movement on the day of collection.

(r) A stool sample for culture, ova and parasite evaluation, and *C. difficile* assay will be obtained at Screening and at any time point during the study when a subject becomes symptomatic, including worsening or return of disease activity.

(s) CCI

(t) For OLE enrollers, subjects should receive their first OLE vedolizumab SC dose as close to Week 14 of MLN0002SC-3031 as possible (preferably within Week 14 ±3 days). If this window is too challenging for the sites, dosing within week 14 ±7 days is acceptable from a PK perspective (ie, maintaining trough concentration at or above 10 µg/mL).

**Appendix A Schedule of Study Procedures (Maintenance Phase)**

Study Procedures	Maintenance Phase (a)																Final Safety Follow-up Visit (b)	Unscheduled Visit (c)
	46-Week Double Blind, Randomized Treatment Period (Week 7 must occur +7 days after Randomization)																	
	Wk 7	Wk 8	Wk 10, 12 (d)	Wk 14	Wk 16, 18, 20 (d)	Wk 22	Wk 24, 26, 28 (d)	Wk 30	Wk 32, 34, 36 (d)	Wk 38	Wk 40, 42, 44 (d)	Wk 46	Wk 48 (d)	Wk 50	Wk 51	Wk 52/ET (s)	Wk 68	
		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days	± 1 week	
<b>Clinic Visit Number</b>	6	7		8		9		10		11		12		13	14	15	16	
Physical examination (e)				X		X		X		X		X		X		X	X	
Vital signs (f)	X	X		X		X		X		X		X		X	X	X	X	
PML checklist (g)		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
PML wallet card																X		
Diary review	X	X		X		X		X		X		X		X		X	X	
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing - Blinded SC		X	X	X	X	X	X	X	X	X	X	X	X	X				
CDAI (h)				X		X		X		X		X		X		X (i)	X	
<b>CCI</b>																		
PRO (IBDQ; EQ-5D)								X								X		
<b>CCI</b>																		
12-lead ECG																X	X	
PTE/AE assessment (k)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE assessment (l)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.



**Appendix A Schedule of Study Procedures (Maintenance Phase) (continued)**

Study Procedures	Maintenance Phase (a)																Final Safety Follow-up Visit (b)	Unscheduled Visit (c)
	46-week Double Blind, Randomized, Treatment Period (Week 7 must occur +7 days after Randomization)																	
	Wk 7	Wk 8	Wk 10, 12 (d)	Wk 14	Wk 16, 18, 20 (d)	Wk 22	Wk 24, 26, 28 (d)	Wk 30	Wk 32, 34, 36 (d)	Wk 38	Wk 40, 42, 44 (d)	Wk 46	Wk 48 (d)	Wk 50	Wk 51	Wk 52/ET (s)		
		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days	± 1 week	
Clinic Visit Number	6	7		8		9		10		11		12		13	14	15	16	
Sample collection for:																		
Serum pregnancy test																X	X	
Urine pregnancy test (m)			wk10	X	wk 18	X	wk 26	X	wk 34	X	wk 42	X		X				
Clinical chemistry				X		X		X		X		X		X		X	X (r)	
Hematology				X		X		X		X		X		X		X (i)	X (r)	
Coagulation						X										X		
Urinalysis																X		
PK assessment (n)	X	X		X		X		X		X		X		X	X	X	X	
CCI																		
Fecal calprotectin (o)								X								X		
CRP								X								X		
<i>C difficile</i> stool sample (p)																	X (p)	
CCI																		

Footnotes are on last table page.

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Footnotes:

Day=day after the first dose in Induction Period. CCI ██████████ HBV=hepatitis B virus, HCV=hepatitis C virus, PML=progressive multifocal leukoencephalopathy

(a) Maintenance period: There should be a minimum of 7 days between 2 consecutive doses.

(b) Subjects discontinued from the study for any reason during the Maintenance Phase will complete the ET Visit, the Final Safety Visit and LTFU. These subjects are not enrolling in the OLE study.

(c) Subjects seen at an unscheduled visit for disease exacerbation or SAE will complete the Unscheduled Visit assessments.

(d) Nonclinic visits. Subject will inject once the site has confirmed the subject can inject via the pre-dose phone call.

(e) Physical examination: Clinically significant findings will be recorded as AEs if they start after the first dose of study drug.

(f) Vital signs: Weight and vital signs will also be measured on dosing days prior to dosing.

(g) PML checklist: will be administered prior to each dosing event. The PML subjective checklist will be administered in person at dosing occurring in the clinic during scheduled visits. The PML subjective checklist will be administered over the phone when the subject is injecting outside of the clinic.

(h) CDAI score components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components.

(i) Hematocrit level from central laboratory results will be used for calculation of the CDAI score.

(j) CCI ██████████

(k) Collection of AEs, to include concomitant medications, will begin following first dose of study drug and will continue through Week 68/Final Safety Visit. To be performed in person at dosing occurring in the clinic during scheduled visit. To be performed over the phone at dosing occurring outside of the clinic.

(l) Collection of all SAEs will continue from Week 7 through Week 68/Final Safety Visit. To be performed in person at dosing occurring in the clinic during scheduled visit. To be performed over the phone at dosing occurring outside of the clinic.

(m) A urine pregnancy test will be completed for all female subjects of child bearing potential on a 4-weekly basis prior to administration of study drug.

(n) PK samples at Weeks 7, 51 and 52 can be collected at any time during the visit. All other PK CCI ██████████ samples will be obtained at predose (within 30 minutes prior to dosing). The

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(o) Fecal calprotectin stool sample should be the first bowel movement on the day of collection.

(p) A stool sample for culture, ova and parasite evaluation, and *C. difficile* assay will be obtained (if indicated) at any time point during the study when a subject becomes symptomatic, including worsening or return of disease activity.

(q) CCI ██████████

(r) If indicated.

(s) Subjects randomized in the Maintenance Phase who complete the study or ET after Week 6 for disease worsening or after Week 14 who require rescue medication will be offered entry into the OLE study after completion of the Week 52/ET assessments. Week 0 of the OLE study should occur no more than 4 weeks after the last dose of study drug for completers/ET.

## 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. If the investigator/institution retains the services of any individual or party to perform study related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study related duties and functions, and should implement procedures to ensure the integrity of the study related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. 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.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. 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.

10. 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.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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### 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 CCI 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.

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## 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.



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**Appendix F 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	Total number of checked boxes (check <b>all</b> that apply): <input type="checkbox"/> Arthritis/arthralgia <input type="checkbox"/> Iritis/uveitis <input type="checkbox"/> Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis <input type="checkbox"/> Anal fissure, fistula, or abscess <input type="checkbox"/> Other fistula <input type="checkbox"/> Fever over 37.8°C during past week		× 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)	$(1 - (\text{Body weight} / \text{Standard Weight})) \times 100$		× 1	
Final Score			Add totals:	

Source: Adapted from: Best WR, Bectel 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.

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

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

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## Appendix H Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 06 are indicated. The corresponding text has been revised throughout the protocol.

### Change 1: Clarification of the Sponsor address in Japan.

The primary change occurs on Page 1:

Initial wording: Takeda Development Center Japan,  
Takeda Pharmaceutical Company Limited,  
1-1, Doshomachi 4-Chome, Chuo-ku Osaka 540-8645, Japan

Amended or new wording: ~~Takeda Development Center Japan,~~  
Takeda Pharmaceutical Company Limited,  
1-1, Doshomachi 4-Chome, Chuo-ku Osaka 540-8645, Japan

### Rationale for Change:

Administrative change to the Sponsor address in Japan.

Section 3.4 Corporate Identification also contains this change.

### Change 2: Administrative change to the Responsible Medical Officer and Approvers.

The primary change occurs in Section 1.1 Contacts and Section 1.2 Approval:

Initial wording: PPD [Redacted]

Amended or new wording: PPD [Redacted]

Initial wording: PPD [Redacted]

Amended or new wording: PPD [Redacted]

Initial wording: PPD [Redacted]



Amended PPD  
or new  
wording:

**Rationale for Change:**

Administrative change to study personnel.

**Change 3:** Inclusion of an additional secondary objective and endpoint, and exploratory endpoint.

The primary change occurs in Sections 5.1.2 Secondary Objectives, 5.2.2 Secondary Endpoints and 5.2.4 Exploratory Endpoints:

Added text: 

- **To assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52, in subjects who are naïve to TNF- $\alpha$  antagonist exposure and achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.**

Added text: 

- **Proportion of TNF- $\alpha$  antagonist naïve subjects who achieved clinical remission, defined as CDAI score  $\leq 150$ , at Week 52.**

Added text: CCI

**Rationale for Change:**

Inclusion of an additional secondary objective and associated endpoints to assess the effect of vedolizumab SC treatment in subjects with no prior TNF- $\alpha$  antagonist exposure, TNF- $\alpha$  exposure, and TNF- $\alpha$  failure.

Section 2.0 STUDY SUMMARY also contains this change.

**Change 4:** Clarification to the Final Visit/Early Termination procedures for subjects who complete (OLE Enroller/Nonenroller) at Week 14 (Induction Phase), and subjects who complete (Week 52) or discontinue from the Maintenance Phase.

The primary change occurs in Section 6.1 Study Design and Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders:

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Initial wording:

- Subjects who achieve a clinical response at Week 6 will be randomized into the Maintenance Phase. Upon completion of the Week 52 assessment or upon early discontinuation due to treatment failure (ie, disease worsening or need for rescue medications) these subjects will be eligible to enter the OLE study.
- Subjects who do not achieve a clinical response at Week 6 will not be randomized in to the Maintenance Phase, and instead will receive a third infusion of vedolizumab IV 300 mg at Week 6. Subjects who achieve a clinical response at Week 14 (by CDAI) will be eligible to enroll in the OLE study, while subjects who do not achieve clinical response will be discontinued.

...

Subjects who do not participate in the OLE trial or are discontinued, will enter the Follow-Up Period and complete a final on-study safety assessment at 18 weeks (ie, 5 vedolizumab half-lives) from the last study drug dose (Week 50 or early termination [ET]).

Additionally, subjects who do not participate in the OLE trial will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.

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- 
- Amended or new wording:
- Subjects who achieve a clinical response at Week 6 will be randomized into the Maintenance Phase. Upon completion of the Week 52 assessment or upon early discontinuation due to treatment failure (ie, disease worsening **after Week 6** or need for rescue medications **after Week 14**) these subjects will be eligible to enter the OLE study (Table 7.a).
  - Subjects who do not achieve a clinical response at Week 6 will not be randomized in to the Maintenance Phase, and instead will receive a third infusion of vedolizumab IV 300 mg at Week 6. Subjects who achieve a clinical response at Week 14 (by partial Mayo score) will be eligible to enroll in the OLE study. **Subjects who respond but choose not to enroll in the OLE study and,** while subjects who do not achieve clinical response **at Week 14** will be discontinued.

...

Subjects who do not participate in the OLE ~~trial~~ **study** or are discontinued **from the study before Week 6**, will enter the Follow-Up Period and complete a final on-study safety assessment at 18 weeks (ie, 5 vedolizumab half-lives) from the last study drug dose (~~Week 50 or early termination [ET]~~).

Additionally, subjects who do not participate in the OLE ~~trial~~ **study or have discontinued before Week 6** will be required to participate in a long-term follow-up (LTFU) safety survey by telephone, 6 months after the last dose of study drug.

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[Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders:](#)

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Description Column labelled *Week 14, Day 99 (±3 days)* split into 2 columns labelled **OLE** of change: **nonenroller** and **OLE enroller**:

- Footnote (t) added:
  - **(t) For OLE enrollers, subjects should receive their first OLE vedolizumab SC dose as close to Week 14 of MLN0002SC-3031 as possible (preferably within Week 14 ±3 days). If this window is too challenging for the sites, dosing within week 14 ±7 days is acceptable from a PK perspective (ie, maintaining trough concentration at or above 10 µg/mL).**
- OLE nonenroller column:
  - X included in rows *Physical examination, Vital signs, PML checklist, Diary review, Concomitant medications and procedures, CCI [REDACTED] CDAI, PTE/AE assessment, SAE assessment, Urine pregnancy test, PK assessment CCI [REDACTED]*
- OLE enroller column:
  - X included in rows *Physical examination, Vital signs, PML checklist, Diary review, Concomitant medications and procedures, Fistula Assessment (if indicated), Assess eligibility for OLE, CDAI, PRO (IBDQ; EQ-5D), CCI [REDACTED], PTE/AE assessment, SAE assessment, and Urine pregnancy test.*

#### Rationale for Change:

Clarification to the Final Visit/Early Termination procedures for subjects who complete (OLE Enroller/Nonenroller) at Week 14 in the Induction Phase, and subjects who complete (Week 52) or ET from the Maintenance Phase.

The following sections also contain this change:

- [Figure 6.a Schematic of Study Design.](#)
- [Section 7.5 Procedures for Discontinuation or Withdrawal of a Subject.](#)
- [Section 9.3.2.1 Nonresponders.](#)
- [Section 9.3.3 Final Visit or ET.](#)
- [Section 9.3.4 Final Safety Follow-up Visit.](#)



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**Change 5:** Clarification to the study design schematic.

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The primary change occurs in [Figure 6.a Schematic of Study Design](#):

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Initial wording: (c) Visit 1 of Extension Study MLN0002SC-3030 is within 1 week of completing Week 52 (Visit 15) procedures. Subjects not randomized into the Maintenance Phase (Week 6 Nonresponders) and respond at Week 14 on vedolizumab IV 300 mg are also eligible for entry into the Extension Study.

---

Amended or new wording: (c) ~~Visit 1~~ **First visit** of Extension ~~OLE~~ Study MLN0002SC-3030 is within ~~14~~ **4 weeks after last dose of study drug for Week 52 completers/ET or 1 week of Week 14 for Week 14 responders** ~~of completing Week 52 (Visit 15) procedures. Maintenance Phase (Week 6 Nonresponders) and respond at Week 14 on vedolizumab IV 300 mg are also eligible for entry into the Extension Study.~~

---

**Rationale for Change:**

Clarification to the timing of the first visit of OLE Study MLN0002SC-3030.

---

**Change 6:** Study design updated to clarify that all endoscopies will be centrally read.

---

The primary change occurs in [Section 6.1 Study Design](#):

---

Initial wording:

**CCI** [Redacted]

---

**CCI** [Redacted]

Prope

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### Rationale for Change:

Study design updated to clarify that all endoscopies will be centrally read.

---

The following sections also contain this change:

- CCI [REDACTED]
- Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders

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### Change 7: Clarification to Inclusion Criterion #11.

---

The primary change occurs in Section 7.1 Inclusion Criteria:

---

Initial wording:	<ul style="list-style-type: none"><li>• Corticosteroids<ul style="list-style-type: none"><li>i. The subject has signs and symptoms of persistently active disease despite a history of a least one 4-week induction regimen that included at dose equivalent to prednisone <math>\geq 30</math> mg daily orally for 2 weeks or intravenously for 1 week, OR</li><li>ii. The subject has had two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions. In Japan, at least 1 failed attempt to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally or intravenously, OR</li><li>iii. The subject has a history of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection).</li></ul></li></ul>
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---

Amended or new wording:	<ul style="list-style-type: none"><li>• Corticosteroids<ul style="list-style-type: none"><li>i. The subject has signs and symptoms of persistently active disease despite a history of a least one 4-week induction regimen that included at dose equivalent to prednisone <math>\geq 30</math> mg daily orally for 2 weeks or intravenously for 1 week, OR</li><li>ii. The subject has had 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions. In Japan, at least 1 failed attempt to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally or intravenously, OR</li><li>iii. The subject has a history of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection).</li><li><b>iv. The subject had a relapse within 3 months of stopping steroids.</b></li></ul></li></ul>
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**Rationale for Change:**

Clarification to the inclusion criterion to include subjects who have relapsed within 3 months of stopping steroids according to the current European Crohn's and Colitis Organization guidelines.

---

**Change 8: Clarification to Exclusion Criterion #5.**

The primary change occurs in Section 7.2.1 [Gastrointestinal Exclusion Criteria](#):

---

Initial wording: 5. The subject has had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.

---

Amended or new wording: 5. The subject has ~~had~~ ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.

---

**Rationale for Change:**

Subjects with past medical history but no current ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine are allowed into the study.

---

**Change 9: Clarification to Exclusion Criterion #15.**

The primary change occurs in Section 7.2.3 [General Exclusion Criteria](#):

---

Initial wording: 15. The subject has chronic hepatitis B virus (HBV) infection\* or chronic hepatitis C virus (HCV) infection.  
\* HBV immune subjects (ie, being hepatitis B surface antigen [HBsAg] negative and hepatitis B antibody positive) may, however, be included.

---

Amended or new wording: 15. The subject has chronic hepatitis B virus (HBV) infection\* or chronic hepatitis C virus (HCV) infection.  
\* HBV immune subjects (ie, being hepatitis B surface antigen [HBsAg] negative and hepatitis B **surface** antibody [**HBsAb**] positive) may, however, be included.

---

**Rationale for Change:**

Clarification to Exclusion criterion text.

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**Change 10: Clarification to Exclusion Criterion #20.**

The primary change occurs in Section 7.2.3 [General Exclusion Criteria](#):

---

Initial wording: 20. The subject has had previous exposure to approved or investigational anti-integrins (eg, natalizumab, efalizumab, etrolizumab, AMG 181), anti-MAdCAM-1 antibodies, or rituximab.

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Amended 20. The subject has had previous exposure to approved or investigational or new anti-integrins **antibodies** (eg, natalizumab, efalizumab, etrolizumab, AMG wording: 181), anti-MAdCAM-1 antibodies, or rituximab.

---

**Rationale for Change:**

Clarification to Exclusion criterion text.

---

**Change 11:** Clarification to the period for excluded medications and treatments.

---

The primary change occurs in Section 7.3 Excluded Medications and Treatments.

---

Initial The following medications are excluded from use during the study:  
wording:

---

Amended The following medications are excluded from use during the study (**from**  
or new **informed consent to Week 68**):  
wording:

---

**Rationale for Change:**

Inclusion to text to outline the specific period for excluded medications and treatments.

---

**Change 12:** Clarification to Section 9.1.5 Vital Signs Procedure.

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The primary change occurs in Section 9.1.5 Vital Sign Procedure:

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Deleted ~~When vital signs are scheduled at the same time as blood draws, the blood draw~~  
text: ~~will take priority and vital signs will be obtained within 0.5 hour before the~~  
~~scheduled blood draw.~~

---

**Rationale for Change:**

There is no time restriction between the timing of the vital sign measurements and blood draws during the same visit.

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**Change 13:** Clarification to Section 9.1.6.1 Diary Completion and Review.

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The primary change occurs in Section 9.1.6.1 Diary Completion and Review:

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Initial wording: Diary entries will be made daily by subjects from screening to end of study, and will be used for CDAI calculation. At 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 a validated electronic system. At each visit, including during screening, the CDAI score must be calculated prior to dosing by the investigator or designee based on daily diaries, laboratory assessments, and clinical examination and recorded in the subject's source documents.

The CDAI score evaluated during screening will be used to determine eligibility, using subject diary entries within 14 days prior to Week 0. <sup>CC</sup>

Amended or new wording: Diary entries will be made daily by subjects from screening to end of study, and will be used for CDAI calculation. At 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 a validated electronic system. At each visit, including during screening, the CDAI score must be calculated prior to dosing by the <sup>CCI</sup>, accessed by the investigator or designee based on daily diaries, laboratory assessments, and clinical examination and recorded in the subject's source documents.

The CDAI score evaluated during screening will be used to determine eligibility, using subject diary entries within 10-14 days prior to Week 0. **At a minimum, 7 days of diary data from the last 10 days prior to Week 0 will be required for the calculation of the score. Subjects will be required to complete diary entries for at least 14 days prior to Week 0.** <sup>CCI</sup>

---

**Rationale for Change:**

Clarification to text that the CDAI score is automatically calculated by the EPX system and not manually calculated by the investigator. Clarification to the number of days of diary data that is required for the CDAI calculation at Screening.

Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders also contains this change.

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**Change 14: ECG procedure updated.**

The primary change occurs in Section 9.1.12 ECG Procedure:

Initial wording: Subjects will be supine and will have rested for 5 or more minutes before any ECG is recorded. Tracings will include subject number and initials and the date and time of recording and all other subject identifiers will be removed or obscured.

Amended or new wording: Subjects will be supine and will have rested for 5 or more minutes before any ECG is recorded. Tracings will include subject number and initials and the date and time of recording and all other subject identifiers will be removed or obscured.

---

**Rationale for Change:**

ECG tracings are source documentation and will not be seen by the sponsor.

---

**Change 15: Addition of a Pre-Week 14 visit for Week 6 nonresponders.**

The primary change occurs in Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders:

Description of change: Additional column labelled **Pre-Week 14, Day 92 (+4 days)**

- ~~X~~ included for *Serum pregnancy test, Clinical chemistry, Hematology, Urinalysis, PK assessment, CCI* Fecal Calprotectin and CRP.

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**Rationale for Change:**

Additional visit so that the safety laboratory samples can be taken so that the results are current and available for the Week 14 visit for Week 6 nonresponders.

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**Change 16:** Update to Appendix A Schedule of Study Procedures for Crohn's disease-related events.

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The primary change occurs in [Appendix A Schedule of Study Procedures: Screening, Induction and Nonresponders](#):

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Description Row labelled *CD-related events* removed.  
of change:

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**Rationale for Change:**

CD-related events removed from the Induction Phase and Maintenance Phase schedules as these are recorded as AEs, SAEs, or concomitant procedures in the eCRF.

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**Change 17:** Update to Appendix B Responsibilities of the Investigator.

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The primary change occurs in Section [Appendix B Responsibilities of the Investigator](#):

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Added text: **3. If the investigator/institution retains the services of any individual or party to perform study related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study related duties and functions, and should implement procedures to ensure the integrity of the study related duties and functions performed and any data generated.**

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**Rationale for Change:**

Update to the Responsibilities of the Investigator in line with Section 4.2.6 of the Guideline for Good Clinical Practice E6 (R2), which was revised on 01 December 2016.

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Protocol Amendment 6 A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Aug-2017 12:23 UTC
	Clinical Pharmacology Approval	25-Aug-2017 15:19 UTC
	Clinical Science Approval	25-Aug-2017 18:50 UTC
	Clinical Approval	28-Aug-2017 14:43 UTC

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