Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy and Safety of Intravenous Vedolizumab (300 mg) Infusion Treatment in Chinese Subjects with Moderately to Severely Active Crohn's Disease

NCT Number: NCT03234907

Protocol Approve Date: 23 April 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy and Safety of Intravenous Vedolizumab (300 mg) Infusion Treatment in Chinese Subjects With Moderately to Severely Active Crohn's Disease

Vedolizumab IV Compared to Placebo in Chinese Subjects With Crohn's Disease

Sponsor:	Takeda Development Center Asia, Pte Ltd 21 Biopolis Road Nucleos North Tower, Level 4 Singapore 138567		
Study Number:	Vedolizumab-3034		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Vedolizumab IV		
Date:	23 April 2019	**Amendment Number:**	03

Amendment History:

Date	Amendment Number	Region
08 July 2015	Initial version	Asia
03 March 2017	01	Asia
21 February 2018	02	Asia
23 April 2019	03	Asia

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

TDC sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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

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

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

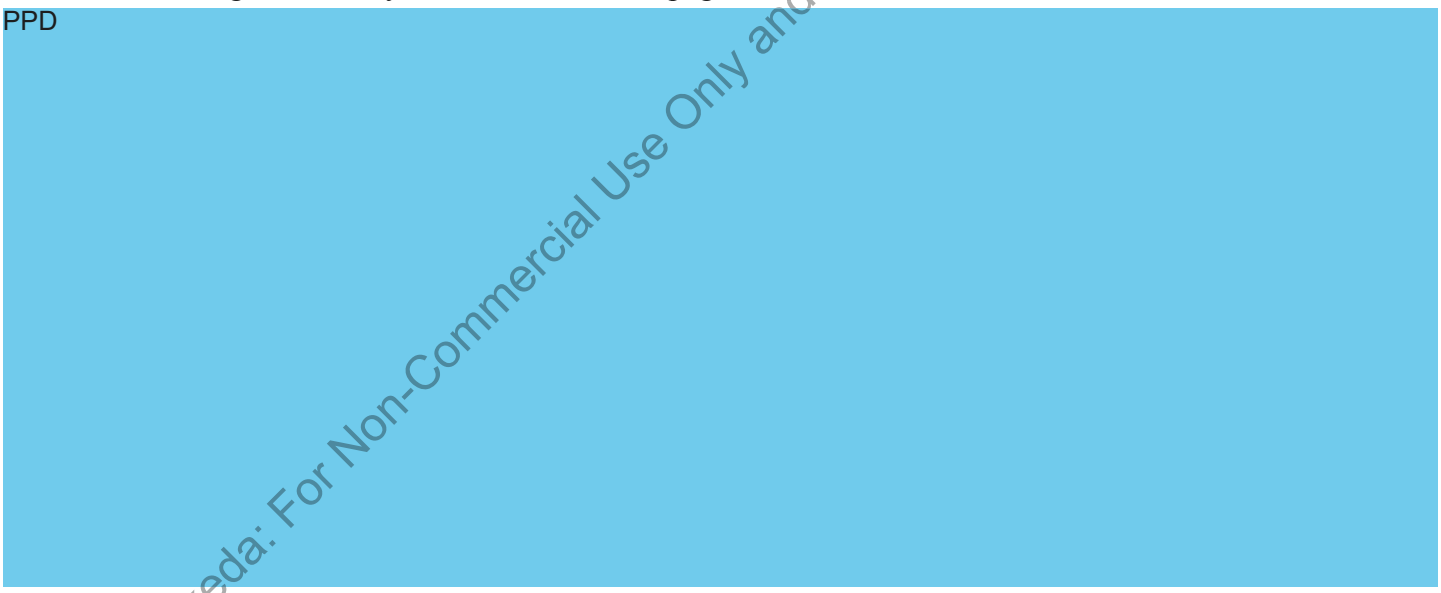
- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

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

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

PPD



INVESTIGATOR AGREEMENT

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

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

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City)

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the Protocol Incorporating Amendment 03.

The primary purpose of this amendment is to update the stratification factors and include a data monitoring committee. The previous protocol amendment (02) has not been implemented at any study site. Additional feedback from the health authority on protocol amendment 02 has been incorporated in protocol amendment 03. Other minor changes in procedures are proposed. Minor grammatical and editorial changes are included for clarification purposes only. For specific descriptions of text changes and where the changes are located, see Appendix G.

Changes in Amendment 03

1. Update to the stratification factors.
2. Inclusion of a data monitoring committee.
3. Addition of definition for sponsor executive committee.
4. Inclusion of maximum sample size.
5. Update schedule of assessment table to include 1 early termination procedure for all subjects.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Asia, Pte. Ltd.	**Compound:** Vedolizumab IV	
Title of Protocol: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy and Safety of Intravenous Vedolizumab (300 mg) Infusion Treatment in Chinese Subjects With Moderately to Severely Active Crohn's Disease	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: Vedolizumab-3034	**Phase:** 3	

Study Design:

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of vedolizumab treatment in Chinese subjects with moderately to severely active Crohn's disease (CD).

Approximately 204 eligible subjects will be enrolled in the induction phase and randomized 1:2 in a double-blinded manner to receive placebo or vedolizumab intravenous (IV) 300 mg at Week 0 (Day 1), Week 2 (Day 15), and Week 6 (Day 43). The primary efficacy evaluation for the induction phase will be performed at Week 10.

The induction study will be conducted using an adaptive statistical design, permitting potential to increase sample size and/or primary endpoint change for the final induction phase analysis. One interim analysis will occur when approximately 144 patients are enrolled into the study and with week 10 observation or early discontinuation from the induction phase. At the interim analysis, enhanced clinical response and clinical remission will be tested and conditional power will be calculated by an independent statistical center (ISC). The data monitoring committee (DMC) will compare the calculated conditional power with the prespecified sample size and primary endpoint adaptation rules to determine the final sample size and primary endpoint for the study. The DMC will recommend to the sponsor executive committee the sample size and primary endpoint adaptation decisions. The sponsor will remain blinded to the interim results until completion of the study.

To adjust for the known confounding factors in the induction phase, subjects' randomization assignment will be stratified by:

- Previous failure of tumor necrosis factor-alpha (TNF-α) antagonist therapy or concomitant use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate).
- Concomitant use of oral corticosteroids.

In the maintenance phase, subjects who received vedolizumab or placebo in the induction phase and achieved clinical response at Week 10 will continue to receive the same treatment as they received in the induction phase once every 8 weeks (Q8W) starting from Week 14 (ie, Weeks 14, 22, 30, 38, 46, and 54) in a double-blinded manner. Subjects who received vedolizumab IV or placebo in the induction phase and did not achieve clinical response at Week 10 will receive vedolizumab once every 4 weeks (Q4W) starting from Week 14 (ie, Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58) in a double-blinded manner. Subjects receiving oral corticosteroids who have achieved clinical response at Week 10 will begin a corticosteroid tapering regimen. Ileocolonoscopy will be performed at screening, Week 10, and Week 60/early termination (ET). All ileocolonoscopy will be centrally read.

No more than 50% of the subjects enrolled in the trial should have previously been exposed to and failed TNF-α antagonist treatment.

Primary Objective:

To assess the effect of vedolizumab IV as induction treatment in Chinese subjects with moderately to severely active CD at Week 10.

<table>
<tr><td colspan="2">Secondary Objective:
To assess the effect of vedolizumab IV on clinical remission in the induction phase in Chinese subjects with moderately to severely active CD at Week 10.</td></tr>
<tr><td colspan="2">Subject Population:
Chinese subjects aged 18 to 80 years, inclusive, with moderately to severely active CD.</td></tr>
<tr><td>Number of Subjects:
Estimated total: Approximately 204 subjects randomized
Vedolizumab IV 300 mg: 136 subjects
Placebo IV: 68 subjects</td><td>Number of Sites:
Estimated total: Approximately 20 sites in China</td></tr>
<tr><td>Dose Level(s):
Vedolizumab 300 mg IV (dose will be administered with modified frequency based on subject response)
Placebo IV</td><td>Route of Administration:
IV</td></tr>
<tr><td>Duration of Treatment:
60 week treatment period</td><td>Period of Evaluation:
This study includes a 4-week screening phase, a 10-week induction phase, a 50-week maintenance phase, and an 18-week safety (ie, 5 vedolizumab half-lives) Follow-up phase starting from the last study drug dose (Week 54 or Week 58/ET). Additionally, subjects will be required to participate in a long-term follow-up safety survey by telephone, 6 months after the last dose of study drug.</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
The subject has a diagnosis of CD established at least 3 months prior to screening by clinical and endoscopic evidence and corroborated by histopathology report.
The subject has moderately to severely active CD defined as a Crohn’s Disease Activity Index (CDAI) score of 220-400.
The subject has CD involvement of the ileum and/or colon, at minimum.
The subject has extensive colitis or pancolitis of >8years duration limited colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit.
The subject has demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents: Corticosteroids, immunomodulators (azathioprine or 6-mercaptopurine), TNF-α antagonists.</td></tr>
<tr><td colspan="2">Main Exclusion Criteria:
The subject has had subtotal or total colectomy.
The subject has a history of >3 small bowel resections or diagnosis of short bowel syndrome.
The subject has received any investigational or approved biologic or biosimilar agent within 60 days or 5 half-lives of screening (whichever is longer).
The subject has had prior exposure to approved or investigational anti-integrins including, but not limited to, natalizumab, efalizumab, etrolizumab, or AMG-181, or mucosal addressin cell adhesion molecule-1 antagonists, or rituximab.
The subject has had previous exposure to vedolizumab.
The subject has clinically significant extra-intestinal infection (eg, pneumonia, pyelonephritis) within 30 days of the initial screening visit, or ongoing chronic infection.
The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist at</td></tr>
</table>

screening or prior to the administration of the first dose of study drug at Week 0.
Main Criteria for Evaluation and Analyses: The primary endpoint of the study is the proportion of subjects with enhanced clinical response (defined as ≥100-point decrease in the CDAI score) at Week 10. The secondary endpoint of the study is the proportion of subjects with clinical remission (defined as CDAI score of ≤150 points) at Week 10.
Statistical Considerations: Cochran-Mantel-Haenszel chi-square test will be used in analyzing the proportion based primary and secondary endpoints in the induction phase.
Sample Size Justification: Assuming an enhanced clinical response (CDAI-100) rate of 48% for vedolizumab and 25% for placebo at Week 10, a sample size of 136 subjects in the vedolizumab group and 68 subjects in the placebo group will provide 90% power at 2-sided 0.05 level of significance. The assumed clinical remission and enhanced clinical response rates are based on a global study of vedolizumab in induction and maintenance treatment of subjects with moderately to severely active CD (C13007) as well as a global study of vedolizumab in induction treatment of subjects with moderately to severely active CD (C13011).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Coordinating Investigator

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

3.3 List of Abbreviations

5-ASA	5-aminosalicylate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate transaminase
AUC_{ss}	area under the serum concentration-time curve over the dosing interval at steady-state
AVA	anti-vedolizumab antibody
$C_{avg,ss}$	average concentration over the dosing interval at steady-state
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFDA	China Food and Drug Administration
$C_{max,ss}$	maximum observed serum concentration at steady-state
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CRP	C-reactive protein
C_{trough}	trough serum concentration
$C_{trough,ss}$	trough serum concentration at steady state
$C_{trough,\ Week\ 10}$	trough serum concentration at Week 10
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	Euro Quality of Life-5D
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCVAb	HCV antibody
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease

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ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	immunoglobin
INR	international normalized ratio
IRB	institutional review board
ISC	independent statistical center
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
JCV	John Cunningham virus
K_2EDTA	potassium ethylenediaminetetraacetic acid
LFT	liver function test
LTFU	long-term follow-up
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PTE	pretreatment event
Q4W	once every 4 weeks
Q8W	once every 8 weeks
RAMP	Risk Assessment and Management Program for PML
SAE	serious adverse event
SAP	statistical analysis plan

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

WFI	water for injection
WPAI	Work Productivity and Activity Impairment

3.4 Corporate Identification

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

3.5 Study Definitions

Clinical remission	Crohn's Disease Activity Index (CDAI) score of ≤150 points.
Clinical response	A ≥70 point decrease in CDAI score from baseline (Week 0).
Disease worsening	A ≥100-point increase in CDAI score from the Week 10 value on 2 consecutive visits and/or reaching a CDAI score ≥220 points.
CCI	[redacted]
Enhanced clinical response	≥100-point decrease in the CDAI score from baseline (Week 0).
CCI	[redacted]

4.0 INTRODUCTION

4.1 Background

4.1.1 Crohn's Disease

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

CD is manifested by asymmetric, and transmural inflammation of the digestive tract. In contrast to the diffuse, superficial, continuous inflammation limited to the colon in UC, the inflammation of CD is focal, may be transmural, and can involve any segment of the GI tract from mouth to anus. The prevalence of CD is approximately 150 per 100,000 of the United States (US) population and approximately 125 per 100,000 of population in Western Europe [1-3] and 21.2 per 100,000 of the population in Japan [4]. It is estimated that CD prevalence in China is about 1.4 cases per 100,000 person-years [5]. The prevalence may be underestimated from hospital based data. Although the prevalence in China is lower than in the West, these figures increase rapidly. Compared to 1990, the nationwide ratio of patients with UC and CD to total hospitalized patients has increased by 2.11 times [6] in 2001 and by 2.78 times [7] in 2003, respectively. In Hong Kong, the incidence of CD tripled over the last 10 years [8].

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, ankylosing 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.

4.1.2 Vedolizumab IV

Vedolizumab (also called MLN0002) is a humanized immunoglobulin (Ig) G1 mAb directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue (GALT) through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [9-12]. Vedolizumab binds the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing leukocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [13]. Vedolizumab has been developed as a treatment for UC and CD, which are characterized by inflammation of the GI tract.

Vedolizumab IV (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; or MLN0002 IV) has been granted marketing approval in several regions, including the US and European

Union, for the treatment of adult patients with moderately to severely active UC or CD who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or a tumor necrosis-alpha (TNF-α) antagonist. The initial approved dosing and administration regimen consists of 300 mg vedolizumab IV infused intravenously, over approximately 30 minutes, at Weeks 0, 2, and 6, then once every 8 weeks (Q8W) thereafter.

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

4.1.2.1 Nonclinical

Nonclinical in vitro and in vivo studies have been conducted with vedolizumab and its murine homologue, Act-1. Act-1 has demonstrated clinical and histomorphologic evidence of efficacy in an animal model of IBD (cotton-top tamarins). Extensive nonclinical evaluations of the cardiovascular, acute, local, subchronic, chronic, immunologic, and reproductive toxicity of vedolizumab in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted and support its clinical development. Nonclinical studies also show that vedolizumab does not antagonize $\alpha_4\beta_1$ integrin [13].

4.1.2.2 Human Experience

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

Different intrinsic and extrinsic factors, including age, body weight, serum albumin, severity of disease state, prior treatment with TNF-α antagonist, coadministration with immunomodulators (including azathioprine, 6-mercaptopurine, methotrexate) or aminosalicylates, did not impact the PK of vedolizumab in subjects with UC or CD based on population PK analysis, as such, no dose adjustment is recommended for any of the above-mentioned covariates. Pharmacokinetics of vedolizumab was similar between Japanese and Western subjects.

As of 19 November 2016, more than 4200 subjects have received at least 1 dose of vedolizumab across all studies in the clinical development program. As of 19 November 2016, vedolizumab exposure has extended for ≥12 months in 1832 subjects, ≥24 months in 1379 subjects, ≥36 months in 1169 subjects, ≥48 months in 862 subjects, ≥60 months in 645 subjects, ≥72 months in 308 subjects, ≥84 months in 32 subjects, and ≥96 months in 22 subjects. Based on the most recent drug shipment data (19 November 2016), the cumulative patient exposure to vedolizumab IV since its marketing approval in May 2014 is estimated to be approximately 77,382 patient-years.

In subjects with moderately to severely active CD (Study C13007), including subjects who had failed treatment with 1 or more therapies including TNF-α antagonists, vedolizumab IV 300 mg at

Weeks 0, 2, and 6 (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 period and maintenance period. The study met its primary endpoint for the induction period, clinical remission at Week 6, but did not meet the second primary endpoint of enhanced clinical response (CDAI-100) at Week 6 in the overall population although the treatment difference favored vedolizumab. The study did meet its primary endpoint for the maintenance period, 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 [14].

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-α antagonists. The primary endpoint of clinical remission at Week 6 in the TNF-α 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-α antagonist naïve [15].

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

Vedolizumab has shown an acceptable and consistent safety profile in clinical trials. In the pivotal phase 3 studies (C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (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%). 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. 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 anti-vedolizumab antibodies (AVAs) 16 weeks following the last dose of vedolizumab. Results from the clinical program to date do not suggest an increased

risk for malignancy with vedolizumab treatment. Overall, the safety profile following long-term treatment with vedolizumab in Study C13008 is consistent with safety in the completed studies.

One death occurred in a vedolizumab-treated subject during Study C13006 and 5 deaths occurred during Study C13007, including 1 death in a placebo-treated subject. As of 19 May 2016, a total of 27 deaths from multiple causes were reported in the vedolizumab clinical development program, including the ongoing long-term Study C13008. Twenty-six of the 27 subjects were randomized to the vedolizumab treatment group. Of these deaths, 14 occurred within 18 weeks of the last dose of vedolizumab in phase 3 clinical studies and 12 occurred more than 18 weeks after the last dose of vedolizumab was administered. The cause of the deaths varied, with the majority considered not to be related to vedolizumab.

Overall, vedolizumab IV was well tolerated in clinical studies.

4.2 Rationale for the Proposed Study

Current treatments have been effective for many patients with IBD 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 the treatment of moderately to severely active CD [16]. However, the efficacy of 5-ASAs in CD has been called into question by a recent meta-analysis [17]. Corticosteroids are often required for 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 [18]. 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 TNF-α, 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 [19-21]. However, efficacy data for both infliximab and adalimumab in CD indicate only a minority of patients having a durable response at 1 year [22,23]. 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) ≥10 mg/L [24,25]. In addition to its modest efficacy, treatment with TNF-α antagonists has been associated with SAEs involving hypersensitivity and infection. Reactivations of latent tuberculosis (TB) [26] and disseminated histoplasmosis have been reported and, in some cases, have been fatal [27]. 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-α_4 ($\alpha_4\beta_7$ and $\alpha_4\beta_1$) integrin antagonist was approved by the US Food and Drug Administration (FDA) in 2008

for use in CD patients who are refractory to standard therapy [28]. 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 (VCAM-1), 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 [29]. The limitations of current therapies for IBD indicate that there is a significant need for safer and more effective therapies.

Vedolizumab is being developed to meet the unmet medical needs in CD treatment in China.

4.2.1 Benefit:Risk Assessment

The proposed study (Vedolizumab-3034) is designed to evaluate the efficacy and safety of vedolizumab IV as induction and maintenance therapy in Chinese subjects with moderately to severely active CD. The dosing and administration regimen and study population in Vedolizumab-3034 are consistent with the approved vedolizumab IV label globally. Overall, vedolizumab has been well tolerated in clinical studies. The procedures performed during the study are part of usual clinical practice. Taking into account the risks associated with procedures and the disease worsening in this population, the benefit-risk profile remains positive for vedolizumab in this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To assess the effect of vedolizumab IV as induction treatment in Chinese subjects with moderately to severely active CD at Week 10.

5.1.2 Secondary Objective

- To assess the effect of vedolizumab IV on clinical remission in the induction phase in Chinese subjects with moderately to severely active CD at Week 10.

5.1.3 Additional Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

- Proportion of subjects with enhanced clinical response (defined as ≥100-point decrease in the CDAI score) in the induction phase at Week 10.

5.2.2 Secondary Endpoint

- Proportion of subjects with clinical remission (defined as CDAI score of ≤150 points) in the induction phase at Week 10.

5.2.3 Additional Endpoints

CCI

[redacted]

CCI

CCI

- **Safety Assessments**
  - Safety assessed by: Adverse events (AEs), SAEs, adverse events of special interest (AESIs), vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis), AEs related to AVA, and results of 12-lead electrocardiograms (ECGs).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of vedolizumab treatment in Chinese subjects with moderately to severely active CD. Moderately to severely active CD is defined as a CDAI score of 220-450 points. No more than 50% of the subjects enrolled in the trial should have previously been exposed to and failed TNF-α antagonist treatment.

This study includes a 4-week screening phase, a 10-week induction phase, a 50-week maintenance phase, and an 18-week safety (ie, 5 vedolizumab half-lives) follow-up phase starting from the last study drug dose (Week 54 or Week 58/early termination [ET]). In addition, subjects will participate in a long-term follow-up (LTFU) safety survey by telephone at 6 months following the last dose, during which information will be collected on events such as infections resulting in hospitalizations, pregnancy, colorectal dysplasia, cancer, CD-related surgeries, and development of PML.

Approximately 204 eligible subjects will be enrolled in induction phase and randomized 1:2 in a double-blinded manner to receive placebo or vedolizumab IV 300 mg at Week 0 (Day 1), Week 2 (Day 15), and Week 6 (Day 43). The primary efficacy evaluation for the induction phase will be performed at Week 10.

The induction study will be conducted using an adaptive statistical design, permitting potential to increase sample size and/or primary endpoint change for the final induction phase analysis. One interim analysis will occur when approximately 144 patients are enrolled into the study and with week 10 observation. At the interim analysis, enhanced clinical response and clinical remission will be tested and conditional power will be calculated respectively by an independent statistical center (ISC). The data monitoring committee (DMC) will compare the calculated conditional power with the prespecified sample size and primary endpoint adaptation rules to determine the final sample size and primary endpoint for the study. The DMC will recommend to the sponsor executive committee the sample size and primary endpoint adaptation decisions. The sponsor will remain blinded to the interim results until completion of the study.

To adjust for the known confounding factors in the induction phase, subjects' randomization assignment will be stratified by:

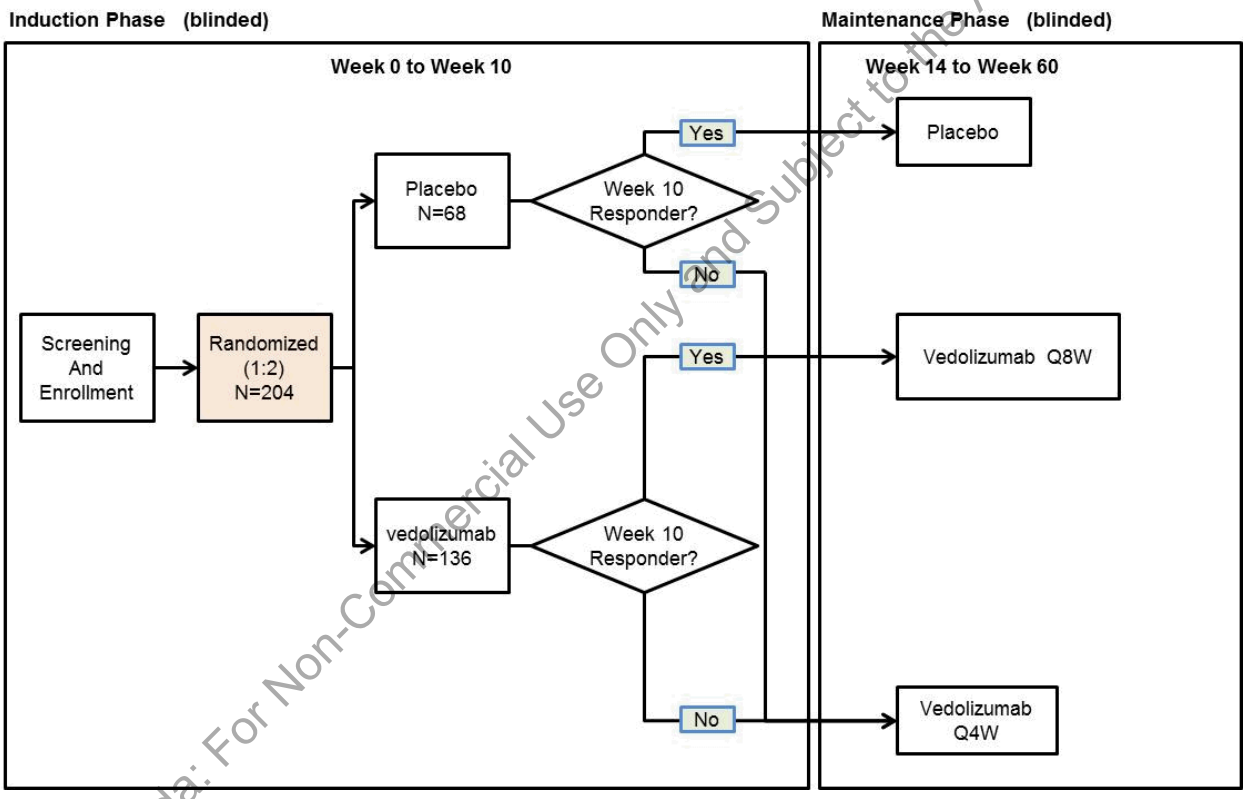
- Previous failure of TNF-α antagonist therapy or concomitant use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate).
- Concomitant use of oral corticosteroids.

In the maintenance phase, subjects who achieved clinical response at Week 10 will continue to receive the same treatment as they received in the induction phase; either vedolizumab starting from Week 14 (ie, Weeks 14, 22, 30, 38, 46, and 54) or placebo in a double-blinded manner. Subjects who received vedolizumab IV or placebo in the induction phase and did not achieve clinical response at Week 10 will receive vedolizumab Q4W starting from Week 14 (ie, Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58) in a double-blinded manner. In order to maintain the

blind, all subjects will receive study drug infusions (placebo or vedolizumab 300 mg) every 4 weeks as detailed in Section 8.1. Subjects receiving oral corticosteroids who have achieved clinical response at Week 10 will begin a corticosteroid tapering regimen. Clinical response is defined as a ≥70 point reduction in CDAI from baseline (Week 0). Evaluation of efficacy for the maintenance phase will be performed at Week 60. Ileocolonoscopy will be performed at screening, Week 10, and Week 60/ET. All ileocolonoscopy will be centrally read.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



Q4W: every 4 weeks; Q8W: every 8 weeks.

6.2 Justification for Study Design, Dose, and Endpoints

Study Design

The study design permits double-blind, placebo-controlled comparison of efficacy and safety parameters between the vedolizumab treatment arm and placebo arm for induction treatment in moderately to severely active CD. Due to the low incidence and prevalence of CD in China and limited study sites, this study is not statistically powered to evaluate the efficacy and safety of

maintenance treatment with vedolizumab IV. Descriptive analyses will be performed for maintenance phase efficacy.

Additional measure will be taken to collect safety parameters beyond the 60-week duration of the trial, where a final visit will be conducted 18 weeks after the last study dose, and additional information will be collected for up to 6 months after the last study dose.

Dose Selection

The strategy for dose selection in this phase 3 study is based on clinical efficacy and dose response in global phase 2 and phase 3 studies, suppression of AVA formation, and serum concentration of vedolizumab at the efficacious doses in phase 2 and 3studies (PK considerations) and maintenance of $\alpha_4\beta_7$ receptor saturation (PD considerations). The dose of 300 mg vedolizumab IV at Weeks 0, 2, and 6 followed by Q8W starting from Week 14 has been tested in global CD phase 3 study (C13007). It is also the dose being used in an ongoing phase 3 CD study in Japan and the recommended dose of vedolizumab IV in countries where vedolizumab is commercially available.

The induction phase efficacy evaluation at Week 10 is based on the results from C13011, which suggested that some CD subjects require an additional dose at Week 6. Results from C13011 showed at Week 6, 19.1% of vedolizumab-treated and 12.1% of placebo-treated subjects were in clinical remission ($p = 0.0478$) and 39.2% of vedolizumab-treated subjects and 22.7% placebo-treated subjects were in enhanced clinical response ($p = 0.0011$). A greater treatment effect was seen at Week 10, with 28.7% and 13.0% of subjects, respectively, achieving clinical remission ($p < 0.002$) and 47.8% and 24.2% of subjects, respectively, achieving enhanced clinical response. Hence, Week 10 is considered a better time point than Week 6 to evaluate the induction phase efficacy.

Endpoints

The primary efficacy endpoint for the induction phase is enhanced clinical response (CDAI-100) at Week 10. This is generally accepted as the standard indicator of disease activity in CD subjects. Cochran-Mantel-Haenszel (CMH) chi-square test will be used in analyzing the proportion based primary and secondary endpoints in the induction phase.

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 compound, such that the risk /benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization or first dose or other.

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 corroborated by a histopathology report. Cases of CD established at least 6 months prior to randomization 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 randomization.
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 9.1.12 Pregnancy.

7. The subject has moderately to severely active CD as determined by a CDAI score of 220 to 400 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 phase, OR
   - Ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each >0.5 cm in diameter) or 10 aphtous ulcerations (involving a minimum of 10 contiguous cm of intestine) consistent with CD, within 4 months prior to randomization, OR
   - Fecal calprotectin >250 µg/g during the screening phase 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.

8. The subject has CD involvement of the ileum and/or colon, at a minimum.
9. The subject has extensive colitis or pancolitis of >8 years duration or limited colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months prior to initial screening (may be performed during screening if not performed in previous 12 months).
10. The subject has a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor must be up-to-date on colorectal cancer surveillance (may be performed during screening).
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:
    - Corticosteroids.
        - Resistance: subjects in whom the response was inadequate after treatment of ≥40 mg/day for ≥1 week (oral or IV), or 30 to 40 mg/day for ≥2 weeks (oral or IV).
        - Dependence: subjects for whom it is difficult to reduce the dosage to <10 mg/day due to recurrence during gradual dose reduction (oral or IV) or subjects had disease recurrence within 3 months after discontinuation of corticosteroids.
        - Intolerance: subjects who were unable to receive continuous treatment due to adverse reactions (eg, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, mood disturbance, infection).
    - Immunomodulators.
        - Refractory: the subject has signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of azathioprine, 6-mercaptopurine, or injectable methotrexate, with a dose of azathioprine ≥0.75 mg/kg/day or 6-mercaptopurine ≥0.5 mg/kg/day, or methotrexate ≥15 mg/week.
        - Intolerance: the subject has a history of intolerance of at least 1 immunomodulators (including but not limited to nausea/vomiting, abdominal pain, pancreatic, liver function test [LFT] abnormalities, lymphopenia, thiopurine S-methyltransferase genetic mutation, hair loss, infection).
    - TNF-α antagonists.
        - Inadequate response: subjects in whom the response was inadequate after the induction therapy in the dosage described in the package insert.
        - Loss of response: recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify).
        - Intolerance: subjects who were unable to receive continuous treatment due to adverse reactions (eg, reaction at administration, drug-induced lupus-like reaction, psoriasis, demyelination disease, congestive heart failure, infection).

7.2 Exclusion Criteria

The exclusion criteria are divided into 3 categories: GI, 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 21 days prior to the administration of the first dose of study drug.
5. The subject has had ileostomy, colostomy, known fixed symptomatic stenosis of the intestine, or evidence of fixed stenosis, or small bowel stenosis with prestenotic dilation.
6. Within 30 days prior to randomization, the subject has received any of the following for the treatment of underlying disease:
   - Nonbiologic therapies (eg, cyclosporine, thalidomide) or traditional Chinese medications other than those specifically listed in the Permitted Medications for the Treatment of CD section.
   - An approved or investigational nonbiologic therapy or traditional Chinese medications in an investigational protocol.
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 had previous exposure to approved or investigational anti-integrins including, but not limited to natalizumab, efalizumab, etrolizumab, or AMG-181, or MAdCAM-1 antagonists, or rituximab.
9. The subject has had previous exposure to vedolizumab.
10. The subject has used topical (rectal) treatment with 5-ASA, corticosteroid enemas/suppositories or traditional Chinese medications for CD treatment within 2 weeks of the administration of the first dose of study drug.
11. The subject requires currently or is anticipated to require surgical intervention for CD during the study.
12. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
13. The subject has a history or evidence of colonic mucosal dysplasia including low or high-grade dysplasia, as well as indeterminate for dysplasia.
14. The subject has a suspected or confirmed diagnosis of ulcerative colitis, indeterminate colitis, ischemic colitis, and radiation colitis.

7.2.2 Infectious Disease Exclusion Criteria

15. The subject has evidence of active infection during the screening period.
16. The subject has evidence of treatment for *Clostridium difficile* infection or other intestinal pathogen with 28 days prior to first dose of study drug.
17. The subject has chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection**.
    * Subjects who are positive for hepatitis B surface antigen (HBsAg) will be excluded.
    For subjects who are negative for HBsAg but are positive for either surface antibodies and/or core antibodies, HBV DNA polymerase chain reaction will be performed and if any test result meets or exceeds detection sensitivity, the subject will be excluded.
    ** If subject is HCV antibody (HCVAb) positive, then a viral load test will be performed. If the viral load test is positive then the subject will be excluded.
18. The subject has active or latent tuberculosis as evidenced by the following:
    - A positive diagnostic TB test within 30 days prior to screening or during the screening period defined as:
      - Positive QuantiFERON test, OR
      - 2 successive indeterminate QuantiFERON tests, OR
      - Chest x-ray within 3 months prior to Week 0 for which the results are suspicious of pulmonary TB.
        Note: Subjects with history of TB who have documented previously treated TB which was successful, with a negative QuantiFERON test, can be included in the study.
19. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
20. The subject has received any live vaccinations within 30 days prior to screening.
21. The subject has a clinically significant extra-intestinal infection (eg, pneumonia, pyelonephritis) within 30 days of the initial screening visit, or ongoing chronic infection.

7.2.3 General Exclusion Criteria

22. The subject has had hypersensitivity or allergies to vedolizumab or its components.
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 enrollment 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 randomization; 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 randomization. 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 randomization.

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 phase:
    - Hemoglobin level <8 g/dL.
    - White blood cell (WBC) count $<3 \times 10^9$/L.
    - Lymphocyte count $<0.5 \times 10^9$/L.
    - Platelet count $<100\times10^9$/L or $>1200\times10^9$/L.
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN).
    - Alkaline phosphatase >3 × ULN.
    - Serum creatinine >2 × ULN.
29. Removed at Amendment 01.
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 opinion of investigator's opinion, may interfere with compliance with study procedures.
32. The subject is unable to attend all study visits or comply with study procedures.
33. The subject is required to take excluded medications listed in Section 7.3.
34. If female, the subject is intending to become pregnant before, during, or within 18 weeks after participating in the study or intending to donate ova during such time period.
35. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.
36. 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.
37. 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.

7.3 Excluded Medications and Treatments

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

- Any treatments 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.)
- 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 ≤30 mg/day, budesonide at a stable dose ≤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 or 6-mercaptopurine 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.
  - Methotrexate provided that the dose has been stable for the 8 weeks immediately prior to first dose of study drug;

  - Antibiotics used for the treatment of CD (ie, 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 corticosteroids, dose reduction should be performed, as per the tapering schedule (see Section 7.3.1.1).
- **Need for rescue medication:** 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. Administration of a rescue medication, approved or investigational, constitutes treatment failure (ie, lack of efficacy) and the subject should be withdrawn from the study according to Section 7.4. 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

Subjects receiving oral corticosteroids who have achieved clinical response at Week 10 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 is reached.
- For prednisone at doses ≤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 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 9.1.19.

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, see Section 9.1.9), if the following circumstances occur at any time during study medication treatment:

     – ALT or AST >8 × ULN, OR

     – ALT or AST >5 × ULN and persists for more than 2 weeks, OR

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, OR

     – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

   - Leukopenia or Lymphopenia: WBC and lymphocyte counts will be monitored for all subjects. Azathioprine, 6-mercaptopurine, or methotrexate, if applicable, should be discontinued and the dose of vedolizumab held for an absolute lymphocyte count $<0.5 \times 10^9$/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of vedolizumab can be administered only if the absolute lymphocyte count is $\geq 0.5 \times 10^9$/L. If the absolute lymphocyte count remains $<0.5 \times 10^9$/L, study drug should be discontinued and the subject withdrawn from the study.

2. Significant protocol deviation. The discovery postrandomization the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

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

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.
7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject, or treatment failure during the maintenance phase, defined as disease worsening (defined as a ≥100-point increase in CDAI score from the Week 10 value on 2 consecutive visits and/or reaching a CDAI score ≥220 points), need for rescue medications (as defined in Section 7.3.1), or need for surgical intervention for treatment of CD.
8. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit and long-term follow-up. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV and Placebo

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

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

All infusions will be administered IV over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on study observations. Subjects will be observed at the clinical site for approximately 2 hours after the completion of the first dose and 1 hour after the completion of subsequent doses 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.

8.1.1.2 Other Protocol-Specified Materials

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

- Sterile WFI, 10 mL container or larger for study drug reconstitution.
- 250 mL 0.9% sodium chloride for injection in polyvinyl chloride IV bag(s) or 250 mL 0.9% sodium chloride in alternative IV bags or bottles listed in the Pharmacy Manual.
- Polyvinyl chloride infusion line or alternative infusion line listed in the Pharmacy Manual.
- Alcohol swabs.
- Syringes.
- Needles (syringe and infusion).
- Infusion pump (optional).
- Needle sharps container.

8.1.2 Storage

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

Vedolizumab IV must be stored at 2ºC to 8ºC (36ºF to 46ºF). Store the vial or syringe in the carton until time of use. A daily temperature log of the drug storage area must be maintained every day. Any temperature excursions must be reported to Takeda; if the site refrigerator goes out of range, or study drug has been stored incorrectly, immediately contact the unblinded clinical research associate.

8.1.3 Dose and Regimen

The dose and regimen for both randomized groups is provided in Table 8.a and Table 8.b. Instructions for reconstitution and blinded administration will be provided in the pharmacy manual.

Table 8.a Dose and Regimen for Induction Phase

Treatment Group	Dose	Treatment Description
A	Placebo IV	Weeks: 0, 2, and 6
B	Vedolizumab IV 300 mg	Weeks: 0, 2, and 6

IV: intravenous.

During the maintenance phase, subjects randomized or assigned to receive vedolizumab Q4W will receive a 300 mg dose of vedolizumab Q4W from Week 14 through Week 58. Subjects randomized or assigned to receive vedolizumab Q8W during the maintenance phase will receive a 300 mg dose of vedolizumab beginning at Week 14 and every other visit thereafter (ie, Weeks 22, 30, 38, 46, and 54). These subjects will receive placebo (250 mL of 0.9% sodium chloride) at the other study visits (ie, Weeks 18, 26, 34, 42, 50, and 58). Subjects randomized or assigned to placebo will receive 250 mL of 0.9% sodium chloride IV Q4W.

Table 8.b Dose and Regimen for Maintenance Phase

Treatment Group	Dose	Treatment Description
C (A: Week 10 Responder)	Placebo IV	Weeks: 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58 (Q4W)
D (A: Week 10 Nonresponder) (B: Week 10 Nonresponder)	Vedolizumab IV 300 mg	Weeks: 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54 and 58 (Q4W)
E (B: Week 10 Responder)	Vedolizumab IV 300 mg and Placebo IV	Weeks: 14, 22, 30, 38, 46, and 54 (Q8W) and Weeks: 18, 26, 34, 42, 50, and 58 (Q8W)

IV: intravenous; Q4W: every 4 weeks; Q8W: every 8 weeks.

8.1.4 Overdose

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

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

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

The investigator or the investigator's designee will access the interactive web response system (IWRS) at screening to register a subject and obtain the subject study number to identify the subjects throughout the study. The investigator or the investigator's designee will utilize the IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. If the subject is randomized to the active treatment arm the medication identification (ID) number of the investigational drug to be dispensed will then be provided by the IWRS by email notification to the unblinded site pharmacist/nurse. To maintain the blind the IWRS will ensure the investigator or designee is unaware if a medication ID has been assigned or not. If sponsor-supplied drug (active vials) is lost or damaged, the site can request a replacement from IWRS by the unblinded site pharmacist/nurse. Refer to IWRS manual provided separately.

At subsequent drug-dispensing visits, the investigator or designee will again contact the IWRS to register the visits. If the subject is on the active treatment arm the medication ID number of the investigational drug to be dispensed will again be provided by the IWRS by email notification only to the unblinded site pharmacist/nurse and the investigator or designee will again be unaware if a medication ID has been assigned or not.

8.3 Randomization Code Creation and Storage

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

8.4 Investigational Drug Blind Maintenance

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

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. 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.

8.6 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 blinded investigator or blinded designee and delegated unblinded pharmacist, must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (vedolizumab IV 300 mg), the appropriate blinded or unblinded 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 unblinded pharmacist.

Upon receipt of sponsor-supplied drug, the appropriate unblinded 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, the unblinded pharmacist should acknowledge the receipt of the shipment. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file (unblinded pharmacy file).

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

- Continuously monitoring expiration dates based on expiry dating provided on the label.
- Monitoring of vedolizumab IV after receipt, during storage and subject administration to ensure that drug does not experience a temperature excursion outside the range specified.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.

- Verifying that required fields are completed accurately and legibly.

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

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

The unblinded pharmacist must record the current inventory of all sponsor-supplied drugs (vedolizumab IV 300 mg) on a drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials, seal, or signature of the person dispensing the drug. 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 in the subject's medical records and on the drug accountability log.

Prior to site closure or at appropriate intervals, an unblinded 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 designated unblinded pharmacist will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

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

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, 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) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (12) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (beats per minute).

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

On dosing days, vital signs are taken predose.

9.1.6 Primary Efficacy Measurement

Due to low incidence and prevalence of CD and limited study sites in China, this study is only statistically powered to detect difference of treatment arm and placebo arm in efficacy for induction phase. Primary efficacy endpoint of this study is enhanced clinical response (CDAI-100) at Week 10. Disease activity for entry into this study and for efficacy assessment throughout the study will be measured by the CDAI, a standard assessment tool to measure CD disease activity in clinical trials. CDAI includes 2 subjective items (number of liquid stools and abdominal pain), and 6 objective items(general well-being, number of extra-intestinal complications, use of antidiarrheal drugs, presence of abdominal mass, hematocrit, and ideal/observed body weight ratio). During screening, subjects will be instructed on how to appropriately complete the diary. Diary entries will be reviewed by site personnel during screening and (prior to dosing, if applicable) at scheduled visits and at any unscheduled visit due to disease exacerbation. A validated electronic system will be used for collection of the patient diary. A CDAI score will be evaluated during screening to determine eligibility, using patient diary entries within 14 days prior to enrollment, and hematocrit results within 28 days prior to first dose.

9.1.6.1 Diary Completion and Review

Diary entries will be made 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 phase. 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 based on daily diaries, laboratory assessments, and clinical examination.

The CDAI score evaluated during screening will be used to determine eligibility, using subject diary entries within 14 days prior to Week 0 and hematocrit results within 28 days prior to Week 0.

The Week 10 total CDAI score will determine whether the subject has achieved clinical response at Week 10 (a ≥70 point decrease in CDAI score from baseline [Week 0]), and will determine the dosing frequency (Q8W or Q4W) in the maintenance phase.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any

medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at 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. The maximum volume of blood at any single visit is approximately 23 mL, and the approximate total volume of blood for the study is 196 mL.

Clinical laboratory tests to be performed in this study are summarized in Table 9.a. Refer to the Schedule of Study Procedures in Appendix A for timing of all assessments. See 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	
	Creatine kinase	Microscopic (to be obtained in the event of positive leukocyte esterase or blood, will include WBCs, RBCs, and cast[s])
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Bicarbonate	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	
Other:		
HIV test	Beta hCG and Urine Pregnancy hCG (female subjects of childbearing potential)	
Hepatitis panel, including HBsAg, HBsAb, HBcAb, and HCVAb [a]	FSH [b]	
CCI [redacted]	*C. difficile*	
AVA		
QuantiFERON for TB		

ALT: alanine aminotransferase; AST: aspartate transaminase; AVA: anti-vedolizumab antibody; CRP: C-reactive protein; FSH: follicle-stimulating hormone; GGT: γ-Glutamyl transferase; HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; hCG: human chronic gonadotropin; INR: international normalized ratio; PT: prothrombin time; RBC: red blood cell; TB: tuberculosis; WBC: white blood cell.
[a] If subject is HCVAb positive, then a viral load test should be performed. If subject is negative for HBsAg but is positive for either surface antibodies and/or core antibodies, HBV DNA polymerase chain reaction will be performed.
[b] FSH level will be obtained for female subject at screening if they are postmenopausal by history (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented) and not surgically sterile. The FSH result must be >40 IU/mL for the subject to be permitted not to use adequate contraception.

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

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 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×ULN in conjunction with total bilirubin >2×ULN.)

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

CCI [redacted]

9.1.11 Contraception and Pregnancy Avoidance Procedure

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

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

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

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

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

Barrier methods (each time the subject has intercourse):

- Male condom PLUS spermicide.
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

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

Hormonal contraceptives:

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

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.

All women of childbearing potential will have a serum pregnancy test during screening and Week 60 or ET visit. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm/ova donation as part of the study procedures (Appendix A). In addition to a negative serum and urine hCG pregnancy test at screening, subjects also must have a negative urine hCG pregnancy test prior to receiving first dose of investigational drug.

9.1.12 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (Vedolizumab IV, Placebo IV) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after drug administration at Week 0 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 and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female

partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

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

9.1.13 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 and all other subject identifiers will be removed or obscured.

CCI

[redacted]

9.1.15 Tuberculosis Screening

All subjects will complete TB screening to determine eligibility. All subjects must complete a QuantiFERON test and chest x-ray during screening. Subjects will be excluded from the study if they have active or latent TB as defined in Section 7.2.

CCI

[redacted]

9.1.17 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.

9.1.18 PML Checklist

Staff will administer the subjective PML checklist during screening to exclude subjects with positive responses from enrolling into the study. During the course of the study, the PML subjective checklist will be administered on the days of physical examination prior to dosing.

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 Risk Assessment and Minimization for PML (RAMP) algorithm described in Section 11.2.1. The symptoms from a positive PML checklist will be recorded as an AE. Additional information and tools for the RAMP can be found in the Study Manual.

CCI

CCI

[redacted]

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

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

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

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

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

9.1.21 Documentation of Randomization

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

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

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 randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.19 for procedures for documenting screening failures.

Procedures to be completed at screening can be found in the Schedule of Study Procedures (Appendix A).

9.3.2 Randomization

Randomization will take place at Week 0 (Day 1).

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IWRS, as described in Section 8.2. Subjects will be instructed on when to take the first dose of investigational drug as described in Section 6.0. The procedure for documenting screening failures is provided in Section 9.1.19.

Eligible subjects will be enrolled in induction phase and randomized 1:2 in a double-blinded manner to receive placebo or vedolizumab IV 300 mg at Week 0 (Day 1), Week 2 (Day 15), and Week 6 (Day 43). The primary efficacy evaluation for the induction phase will be performed at Week 10.

To adjust for the known confounding factors within treatment arms in the induction phase, subjects' randomization assignment will be stratified by:

- Previous failure of TNF-α antagonist therapy or concomitant use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate).
- Concomitant use of oral corticosteroids.

In the maintenance phase, subjects who received vedolizumab or placebo in the induction phase and achieved clinical response at Week 10 will continue to receive the same treatment as they received in the induction phase Q8W starting from Week 14 (ie, Weeks 14, 22, 30, 38, 46, and 54) in a double-blinded manner. Subjects who received vedolizumab IV or placebo in the induction phase and did not achieve clinical response at Week 10 will receive vedolizumab Q4W starting from Week 14 (ie, Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, and 58) in a double-blind manner. Subjects receiving oral corticosteroids who have achieved clinical response at Week 10 will begin a corticosteroid tapering regimen. Clinical response is defined as a ≥70 point reduction in CDAI from baseline (Week 0). Evaluation of efficacy for the maintenance phase will be performed at Week 60.

No more than 50% of the subjects enrolled in the trial should have previously been exposed to and failed TNF-α antagonist treatment.

Randomization will be handled by the IVRS.

9.3.3 Final Visit or Early Termination

The final visit will be performed on Week 60 or at the ET visit.

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

9.3.4 Final Safety Follow-up Visit

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 60 visit.

9.3.5 Poststudy 6-Month Long-Term Follow-up Survey

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

9.3.6 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 procedures:

- 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.
- AVA sample collection.
- Fecal calprotectin (if indicated).
- *C. difficile* (if indicated).

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

9.3.7 Poststudy Care

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

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses versus 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 PTE(s) or as AE(s).

Laboratory values and ECG findings:

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

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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs/serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

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

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

Table 10.a Takeda Medically Significant AE List

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

AE: adverse event.

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

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

10.1.13 Outcome

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

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 Week 0 (Day 1) 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 at Week 0 (Day 1). Routine collection of AEs will continue until 18 weeks after last dose of study medication.

10.2.1.2 PTE and AE Reporting

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

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

1. Event term.
2. Start and stop date.
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.

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10.2.1.3 AE 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 will not be collected as AEs. These characteristics of disease activity will be regularly captured in the CDAI.

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

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

10.2.1.4 Special Interest AE Reporting

If this special interest AE, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be recorded in a special interest AE eCRF Form 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 infusion-related 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.

During clinic visits, vedolizumab IV should be administered in the presence of a health care professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measure should be available for immediate use. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

If signs or symptoms of an infusion-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 infusion-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 Study Manual).

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

Serious Infection

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

Malignancy

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

Other

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

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

10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE form must be completed, in 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 form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

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

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

10.2.3 Reporting of Abnormal Liver Function Tests

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

If a subject is noted to have ALT or AST >3 × ULN and total bilirubin >2 × ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.9 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 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 DMC

At the interim analysis, enhanced clinical response and clinical remission will be tested and conditional power will be calculated respectively by an independent statistical group who will deliver the results to the DMC. The DMC will compare the calculated conditional power with the prespecified sample size and primary endpoint adaptation rules to determine the final sample size and primary endpoint for the study. The DMC will recommend to the sponsor executive committee the sample size and primary endpoint adaptation decisions. The operational study team will remain blinded to the interim results until completion of the study.

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 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 [33,34]. Natalizumab is a pan-α_4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to VCAM-1 and MAdCAM-1 [35,36]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [13] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical trials with vedolizumab to date, a risk of PML cannot be ruled out.

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

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

To ensure success of the RAMP program, site personnel will be trained to recognize the features of PML, and subjects will be trained to report specific neurological signs and symptoms without

delay. Educational materials for teaching site personnel and subjects about PML and the RAMP procedures will be distributed to all sites and are included in the Study Manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Subjects will receive training and educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

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 CRFs (Electronic)

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

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

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. Reasons for significant corrections should additionally be included.

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

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

12.2 Record Retention

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

application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to 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.

For the purpose of statistical analyses, the induction and maintenance phases will be treated as 2 independent studies. The analysis of the induction phase will formally evaluate and provide conclusive evidence of the efficacy and safety of 300 mg Vedolizumab versus placebo as an induction therapy.

The analysis of the combined induction and maintenance phase data will be exploratory and descriptive in nature.

A blinded data review will be conducted prior to unblinding of randomized 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 (FAS), also known as the ITT population, for the induction phase consists of all randomized subjects who received any amount of blinded study drug. Subjects in this set will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

The FAS for the combined induction and maintenance phase FAS consists of all the randomized subjects who received any amount of maintenance phase study drug. The subjects will be analyzed according to the treatment they were randomized to and the Week 10 response status in order to characterize subjects' straight-through experience in the combined induction and maintenance phase.

The per-protocol (PP) population is a subset of the FAS. 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 per-protocol population dataset will be made prior to the unblinding of the study. Analyses using the per-protocol population may be provided as a sensitivity analysis.

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

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, SD, 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

For the induction study, 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 and placebo groups for the primary and secondary endpoint, closed sequential testing procedure will be used. The secondary endpoint will not be formally tested if the primary endpoint testing result is negative. Multiplicity will not be adjusted across additional endpoints.

All dichotomous efficacy endpoints will be analyzed using CMH tests for risk differences, stratified by:

- Previous failure of TNF-α antagonist therapy or concomitant use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate).
- Concomitant use of oral corticosteroids.

All subjects with missing data for determination of endpoint status will be considered as a nonresponder in the analysis.

To evaluate the robustness of the efficacy results, sensitivity analyses will be conducted via using different approaches on missing data (such as last observation carried forward, etc); adjusting for baseline covariates via logistic regressions, etc. Further details will be provided in the SAP.

For the maintenance study, descriptive and exploratory analyses on efficacy will be conducted.

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13.1.5 Safety Analysis

Safety analysis will be performed using the Safety Analysis Set. No statistical inference will be made for safety analyses. Safety summary will cover both induction and maintenance phase of the study.

The number and percentage of subjects with treatment-emergent adverse events (TEAEs, defined as any AEs newly occurring or worsening during first dose and 18 weeks after last dose of study treatment, regardless of relationship to study drug), AESIs (ie, serious infections, PML, malignancies, liver injury, infusion reactions, injection site reactions), and SAEs which occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug will be summarized by 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 AEs overall and by severity. Change from baseline in clinical laboratory tests and vital signs will be summarized by treatment group. Subjects with markedly abnormal values for laboratory tests and vital signs will be tabulated.

In addition to summarize the AE data by incidence, exposure adjusted AE rates will also be presented.

Long-term safety follow-up data will be summarized descriptively. The CCI [redacted] infusion reactions and safety will be summarized.

13.2 Interim Analysis and Criteria for Adaptation

A single interim analysis is planned for this study with the objective of a potential sample size adjustment and endpoint change. The interim analysis will be conducted after approximately the first 144 subjects (96 subjects in the vedolizumab arm and 48 subjects in the placebo arm) have been enrolled and have completed the Week 10 observation or discontinued from the induction phase early.

Based on this interim analysis, the sample size may be increased if the observed treatment effect for enhanced clinical response is promising but not large enough to yield the likely conclusion of statistical significance at the end of the study using the original planned sample size; in addition, primary endpoint may be changed [37] if the conditional power for clinical remission is much better than that for enhanced clinical response. It is also possible that the entire study design remain unchanged as a result of the interim analysis. Due to low prevalence of CD and limited study sites in China, the primary endpoint in this study is partially different from the global studies. To lower the risk of such a change, the adaptive approach will make the China study be closer to a global study which used clinical remission as one of the co-primary endpoints.

The interim analysis will be conducted by an ISC and presented for review to the DMC. The interim results will not be shared with the sponsor. During the closed session of the DMC meeting, the DMC will compare the conditional power for both enhanced clinical response and clinical remission based on the interim results with the prespecified sample size and primary endpoint adaptation rules and recommend to the sponsor executive committee the final adaptation decision. This recommendation will be documented in the DMC closed meeting minutes.

The sponsor executive committee—individuals identified by Takeda who have the clinical, statistical, and business expertise needed to make critical decisions for Takeda, but who will not have any direct involvement with the study—will meet to review the recommendation. The sponsor executive committee will make a decision to accept or reject the DMC's recommendation and will relay its decision to the DMC.

The sponsor executive committee will inform the study team of the final total sample size only. That is, the study team will remain blinded to the adaptation decision of the primary endpoint until the study database is unlocked for the final induction study analysis.

The final induction phase efficacy and safety analysis will be performed when the induction treatment is completed for the enrolled number of patients as determined by the sample size adaptation rule in the interim analysis. If the decision is made by Takeda to conduct the efficacy and safety induction analyses, the analyses will be performed when the induction treatment is completed for last subject. Results of the induction phase will be submitted to the China Food and Drug Administration (CFDA). The Cui-Hung-Wang test statistic [38] for the first and second stage test statistics will be used for testing the primary endpoint and the conventional test statistic will also be calculated as a sensitivity analysis. The formal proof of strong type I error rate control due to the potential sample size and primary endpoint adaptation in the study design will be included in the SAP.

In such a case, to protect integrity of the maintenance study, the final induction phase analysis will be conducted by an independent statistical team which members will not be involved in the daily study management activities. The final induction phase analysis results will be available to an unblinded team consisted of selected people from needed functions. The unblinded team will summarize the results and submit them to CFDA. Study team members who are not in the unblinded operations as well as study investigators from study sites will not have access to unblinded patient level data from both induction and maintenance phase until the end of the study.

Supplemental efficacy and safety results including both the induction phase and maintenance phase will be analyzed at the end of the study and submitted to CFDA. The final safety follow-up visit will occur 18 weeks after the last study drug dose.

If the decision is made by Takeda to not conduct the efficacy and safety analyses until after the maintenance phase is completed, the study data will be available to the study team and the investigators only after the database lock at the end of the study.

13.3 Determination of Sample Size

The assumed clinical remission and enhanced clinical response rates are based on a global study of vedolizumab IV in induction and maintenance treatment of subjects with moderately to severely active CD (C13007) as well as a global study of vedolizumab in induction treatment of subjects with moderately to severely active CD (C13011).

The sample size calculation is based on the adaptive sample size re-assessment approach [39]. The study is initially powered on an optimistic assumption that the effect size will be similar to what was observed in study C13011 for enhanced clinical response: with assuming enhanced response rate of 48% for vedolizumab and 25% for placebo at Week 10, a sample size of 136 subjects in the vedolizumab group and 68 subjects in the placebo group will provide 90% power at 2-sided 0.05 level of significance.

At the interim analysis, the conditional power based on enhanced clinical response and clinical remission at week 10 will be calculated. If the conditional power for enhanced clinical response

falls in the favorable zone or if it is no less than the conditional power for clinical remission, the enhanced clinical response will remain as the primary endpoint. Otherwise, clinical remission will become the primary endpoint. Once the primary endpoint is determined, sample size will be re-assessed according to a prespecified adaptation rule for the selected endpoint, with a maximum sample size of 300 subjects (200 subjects in the vedolizumab group and 100 subjects in the placebo group). If the conditional power falls in the futility zone, the study will stop for futility; if it falls in the unfavorable zone or favorable zone, no change to sample size will be made; if it falls in the promising zone, sample size will be increased.

The sample size adaptation rule is a prespecified stepwise function to avoid the back calculation problem because 1 sample size can correspond to either barely promising or highly promising interim results. Both the sample size and endpoint adaptation rule will be designed by the sponsor independent design statistician and approved by the sponsor head of biostatistics. Both the sponsor independent design statistician and sponsor head of biostatistics are not involved in the study conduct.

The adaptation rules will be a separate document and will not be accessible to the sponsor study team until completion of the study. It will only be available to the sponsor independent design statistician, the sponsor head of biostatistics, the DMC, and the statistics representative in the sponsor executive committee (if different from the sponsor head of biostatistics).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures

Study Procedure		Screening	Induction Phase				Maintenance Phase												At Completion/ET	18 Weeks After Final Dose	Un-Scheduled Visit [d]
	Week		0 [b]	2	6	10	14	18	22	26	30	34	38	42	46	50	54	58	60/ ET [c]		
	Day	-28 to -1	1 [b]	15	43	71	99	127	155	183	211	239	267	295	323	351	379	407	421/ ET [c]		
	Time window (days) [a]	—	—	±2	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	
	VISIT	1	2 [b]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ ET [c]	19	
Informed consent		X																			
Register subject in IWRS		X																			
Inclusion criteria/exclusion criteria		X [e]	X																		
Demographic data		X [e]																			
Medical and CD history		X																			
Prior CD therapies		X																			
Physical examination [f]		X [e]	X	X	X	X	X				X				X				X	X	X
Vital signs [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X [e]																	X	X	
Chest x-ray		X [e]																		X	
QuantiFERON test		X [i]																			
PML checklist [h]		X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PML wallet card			X																X		
Randomization			X																		
Study drug assignment and administration/register IWRS visit			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X			
Fistula assessment (if indicated) [j]		X	X		X		X		X		X		X		X		X		X		
Laboratory test	Blood biochemistry	X [i]	X	X	X	X	X		X		X		X		X		X		X	X	X
	Hematology	X [i]	X	X	X	X	X		X		X		X		X		X		X	X	X
	Hematocrit	X [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	Coagulation	X [i]				X													X		
	Urinalysis	X [i]	X			X	X												X	X	
	Serum pregnancy test [l]	X [i]																	X	X	

Study Procedure		Screening	Induction Phase				Maintenance Phase												At Completion/ET	18 Weeks After Final Dose	Un-Scheduled Visit [d]
	Week		**0** [b]	**2**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**54**	**58**	**60/ ET** [c]		
	Day	**-28 to -1**	**1** [b]	**15**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**	**323**	**351**	**379**	**407**	**421/ ET** [c]		
	Time window (days) [a]	**—**	**—**	**±2**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	
	VISIT	**1**	**2** [b]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18/ ET** [c]	**19**	
	FSH [m]	X [i]																			
	Urine pregnancy test [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	HBV, HCV, HIV screening	X [i]																			
	Fecal calprotectin [n]	X				X					X								X		X
	CRP	X	X			X					X								X		
	C. difficile stool sample	X [o]																			X [o]
CDAI score [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CCI																					
CCI																					
Diary instruction [r]		X																			
CCI																					
CCI																					
CCI																					
CCI																					
Concomitant medication/concomitant nondrug therapy		X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PTE/AEs [t]		X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE assessment		X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE: adverse event; AVA: anti-vedolizumab antibody; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C-reactive protein; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; CCI [redacted] IWRS: interactive web response system; PML: progressive multifocal leukoencephalopathy; PTE: pretreatment event; SAE: serious adverse event; WPAI: Work Productivity and Activity Impairment.

[a] The date of the first dose of study drug in the induction phase is Week 0 (Day 1). The acceptable time windows are given as the number of days away from each scheduled visit.

[b] All baseline (Week 0) assessments will be done predose.

[c] Examinations to be performed at discontinuation must be performed in subjects who prematurely withdraw from the study in the induction and maintenance phases.

[d] Unscheduled visit will be made due to worsening of CD, etc. Additional tests will be performed as required.

[e] Can be conducted between Day -28 and Day -1.

[f] Physical examination: Clinically significant findings will be recorded as concurrent conditions if start prior to signing the informed consent, or as PTEs if start after signing of the informed consent and as AEs if starts after the first dose of study drug.

[g] 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.

[h] On the days of study drug administration, procedure to be performed before administration of study drug.

[i] The test results should be obtained by Visit 2 (Week 0).

[j] Fistula assessment: The presence of a draining fistula (per the CD activity assessment) will trigger a specific fistula assessment at that visit and at each subsequent visit until Week 60/ ET, even if the fistula has closed in the interim.

[k] Hematocrit will be measured at central laboratory (in addition to scheduled hematology tests) within 10 days before CDAI score evaluation. Hematocrit level from screening could be used for CDAI score that determine eligibility at Week 0.

[l] Will be performed only in women of childbearing potential.

(m) FSH level will be obtained for female subjects at screening if they are postmenopausal by history (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented) and not surgically sterile. The FSH result must be 40>IU/L for the subject to be permitted not to use adequate contraception.

[n] Fecal calprotectin stool sample should be the first bowel movement on the day of collection.

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

[p] CDAI score components are to be performed prior to dosing; the total 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.

[q] To be performed prior to dosing.

[r] Performed prior to administration of study drug.

CCI [redacted]

[t] A PTE is an event occurred before the first dose of study drug. An AE is an event occurred after the first dose of study drug.

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 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 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 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 eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

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

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. 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.
24. 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.

25. 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.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E 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 **all** that apply): ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Anal fissure, fistula, or abscess ☐ Other fistula ☐ 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 – (Body weight/ Standard Weight)) × 100		× 1	
Final Score			Add totals:	

Source: Adapted from: Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70 (3):439-44.
CDAI: Crohn's Disease Activity Index.
[a] If hematocrit subtotal <0, enter 0.
[b] If body weight subtotal <-10, enter -10.

Appendix G Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Update to the stratification factors.

The primary change occurs in Section 6.1 Study Design.

Initial wording:	To adjust for the known confounding factors in the Induction Phase, subjects' randomization assignment will be stratified by: • Previous failure of TNF-α antagonist therapy. • Concomitant use of oral corticosteroids.
Amended or new wording:	To adjust for the known confounding factors in the induction phase, subjects' randomization assignment will be stratified by: • Previous failure of TNF-α antagonist therapy **or concomitant use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate)**. • Concomitant use of oral corticosteroids.

Rationale for Change:

To keep in line with previous protocol amendment 01, as all recruitment was completed for the study before modification of the stratification factor in protocol amendment 02.

The following section also contains this change:

- Section 2.0 STUDY SUMMARY
- Section 9.3.2 Randomization.
- Section 13.1.3 Efficacy Analysis

Change 2: Inclusion of a data monitoring committee.

The primary change occurs in Section 11.1 DMC:

Added text:	**11.1 DMC** **At the interim analysis, enhanced clinical response and clinical remission will be tested and conditional power will be calculated respectively by an independent statistical group who will deliver the results to the DMC. The DMC will compare the calculated conditional power with the prespecified sample size and primary endpoint adaptation rules to determine the final sample size and primary endpoint for the study. The DMC will recommend to the sponsor executive committee the sample size and primary endpoint**

adaptation decisions. The operational study team will remain blinded to the interim results until completion of the study.

Rationale for Change:
To keep in line with previous protocol amendment 01, as the interim analysis was triggered prior to CDE's feedback on protocol amendment 02.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Study Design.
- Section 13.2 Interim Analysis and Criteria for Adaptation.
- Section 13.3 Determination of Sample Size.

Change 3: Addition of definition for sponsor executive committee.

The primary change occurs in Section 13.2 Interim Analysis and Criteria for Adaptation.

Initial wording:	[…] The interim analysis will be conducted by an independent statistical center (ISC). The interim results will not be shared with the sponsor. The independent statistician will compare the conditional power for both enhanced clinical response and clinical remission based on the interim results with the prespecified sample size and primary endpoint adaptation rules and recommend to the sponsor the final adaptation decision. […]
Amended or new wording:	[…] The interim analysis will be conducted by an independent statistical center (ISC) **and presented for review to the DMC**. The interim results will not be shared with the sponsor. ~~The independent statistician~~ **During the closed session of the DMC meeting, the DMC** will compare the conditional power for both enhanced clinical response and clinical remission based on the interim results with the prespecified sample size and primary endpoint adaptation rules and recommend to the sponsor **executive committee** the final adaptation decision. **This recommendation will be documented in the DMC closed meeting minutes.** **The sponsor executive committee—individuals identified by Takeda who have the clinical, statistical, and business expertise needed to make critical decisions for Takeda, but who will not have any direct involvement with the study—will meet to review the recommendation. The sponsor executive committee will make a decision to accept or reject the DMC's recommendation and will relay its decision to the DMC.**

The sponsor executive committee will inform the study team of the final total sample size only. That is, the study team will remain blinded to the adaptation decision of the primary endpoint until the study database is unlocked for the final induction study analysis.

[…]

Rationale for Change:

To provide a definition of the sponsor executive committee and its role within the study.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Study Design.
- Section 13.3 Determination of Sample Size.

Change 4: Inclusion of maximum sample size.

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

Initial wording:

[…]

At the interim analysis, the conditional power based on enhanced clinical response and clinical remission at week 10 will be calculated. If the conditional power for enhanced clinical response falls in the favorable zone or if it is no less than the conditional power for clinical remission, the enhanced clinical response will remain as the primary endpoint. Otherwise, clinical remission will become the primary endpoint. Once the primary endpoint is determined, sample size will be re-assessed according to a prespecified adaptation rule for the selected endpoint. If the conditional power falls in the unfavorable zone or favorable zone, no change to sample size will be made; if it falls in the promising zone, sample size will be increased.

[…]

Amended or new wording:

[…]

At the interim analysis, the conditional power based on enhanced clinical response and clinical remission at week 10 will be calculated. If the conditional power for enhanced clinical response falls in the favorable zone or if it is no less than the conditional power for clinical remission, the enhanced clinical response will remain as the primary endpoint. Otherwise, clinical remission will become the primary endpoint. Once the primary endpoint is determined, sample size will be re-assessed according to a prespecified adaptation rule for the selected endpoint**, with a maximum sample size of 300 subjects (200 subjects in the vedolizumab group and 100 subjects in the placebo group)**. If the conditional power falls in **the futility zone, the study will stop for futility; if it falls in** the unfavorable zone

or favorable zone, no change to sample size will be made; if it falls in the promising zone, sample size will be increased.

[…]

Rationale for Change:
To keep in line with previous protocol amendment 01, as the interim analysis was triggered prior to CDE's feedback on protocol amendment 02, and the adaptation rule was developed based on protocol amendment 01.

Change 5: Update schedule of assessment table to include 1 early termination procedure for all subjects.

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

Initial wording:	(c) Examinations to be performed at discontinuation must be performed in subjects who prematurely withdraw from the study in the induction phase after receiving at least 1 dose. (d) Examinations to be performed at discontinuation must be performed in subjects who prematurely withdraw from the study in the maintenance phase.
Amended or new wording:	[c] ~~Examinations to be performed at discontinuation must be performed in subjects who prematurely withdraw from the study in the induction phase after receiving at least 1 dose.~~ [d] Examinations to be performed at discontinuation must be performed in subjects who prematurely withdraw from the study **in the induction and maintenance phases**.

Rationale for Change:

Removal of ET visit specifically for subjects in the induction phase to keep 1 ET procedure for all subjects regardless of study phase.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	10-Jul-2019 08:09 UTC
	Clinical Science Approval	10-Jul-2019 11:24 UTC
	Biostatistics Approval	10-Jul-2019 14:13 UTC