Title: A Randomized Double-Blind Phase 4 Study to Evaluate the Safety and Proportion of Subjects With Fistula Healing in 2 Dose Regimens of Entyvio (Vedolizumab IV) in the Treatment of Fistulizing Crohn's Disease (ENTERPRISE)

NCT Number: NCT02630966

Protocol Approve Date: 20 April 2017

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 AMENDMENT

A Randomized Double-Blind Phase 4 Study to Evaluate the Safety and Proportion of Subjects With Fistula Healing in 2 Dose Regimens of Entyvio (Vedolizumab IV) in the Treatment of Fistulizing Crohn's Disease (ENTERPRISE)

Vedolizumab IV 300 mg in the Treatment of Fistulizing Crohn's Disease

Sponsor: Takeda Development Center Americas, Inc.
One Takeda Parkway
Deerfield, IL 60015

Takeda Development Centre Europe, Ltd.
61 Aldwych
London, WC2B 4AE
United Kingdom

Study Number: Vedolizumab-4003

IND Number: 009125 **EudraCT Number:** 2015-000852-12

Compound: Vedolizumab IV

Date: 20 April 2017 **Amendment Number:** 05

Amendment History:

Date	Amendment Number	Amendment Type	Region
02 September 2015	Initial Protocol, Version 1	Not applicable	Global
29 February 2016	Amendment 01, Version 1	Substantial	Global
06 May 2016	Amendment 02, Version 1	Non-substantial	Global
11 May 2016	Amendment 03, Version 1	Non-substantial	France
08 July 2016	Amendment 04, Version 1	Non-substantial	France
20 April 2017	Amendment 05, Version 1	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

Contact Type/Role	United States/Canada Contact	Europe Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protoco 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 study protocol and also in accordance with the following:

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

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

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

PPD

1.3 Protocol Amendment 05 Summary of Changes

Rationale for Amendment 05

This document describes the changes in reference to the Protocol Incorporating Amendment 5.

The primary reasons for this amendment are to update the protocol to remove the eligibility requirement for a seton to be placed before randomization, to clarify inclusion and exclusion criteria, to revise the sample size calculation, to add a futility analysis, and to consolidate local country (France) modifications into a single global amendment. Other minor clarifications for procedures are included. Minor grammatical, editorial, and formatting changes, for clarification purposes only, are not listed below nor in Appendix K. For specific descriptions of text changes and where the changes are located, see Appendix K.

Changes in Amendment 05

1. Removed the requirement for perianal seton placement as part of standard of care before randomization.
2. Changed the requirements for seton removal, if applicable, from 10 to 22 weeks after randomization to 6 to 14 weeks after randomization.
3. Added a secondary endpoint to evaluate fistulas healed at both Week 22 and Week 30.
4. Modified inclusion criterion 6 such that both France-specific and global language is presented.
5. Modified inclusion and exclusion criteria to allow additional types of antibiotic to reduce the incidence of abscess.
6. Modified inclusion criteria 10 and 11 per updated safety language.
7. Modified exclusion criteria 6 and 7 per updated safety language.
8. Modified exclusion criterion 17 to remove the option of 5 half lives as washout window.
9. Modified exclusion criterion 19 to also exclude subjects with prior exposure to etrolizumab or anti-mucosal addressin cell adhesion molecule-1 therapy therapy.
10. Reduced the study sample size from 126 (63 per group) to 100 (50 per group).
11. Increased the number of study sites from 30 to 40.
12. Added a stratification factor for seton or no seton at randomization.
13. Added a futility analysis after 25 subjects complete the primary endpoint assessment (Week 30).
14. Updated background information per the current Investigator's Brochure.
15. Revised the rationale for the proposed study given that perianal seton replacement no longer required.
16. Revised the benefit-risk assessment given that perianal seton replacement no longer required.

17. Modified the Schematic of Study Design given the changes in this amendment.
18. Changed the maximum dose of oral corticosteroids from 30 to 20 mg/day and clarified that tapering schedule provided is an example of one schedule; allowed for return to baseline corticosteroid dose.
19. Modified the criteria for discontinuation or withdrawal to add monitoring for leukopenia and lymphopenia and to clarify other criteria.
20. Clarified the medical history collection of smoking/nicotine usage status and collection of all medications for Crohn's disease.
21. Clarified vital signs collection.
22. Clarified that all fistula draining assessments are preferably be done by the same qualified designee.
23. Clarified that confirmation from a central reader is required for magnetic resonance imaging eligibility.
24. Added the *superficial* category for the Parks classification.
25. Clarified the neutralizing anti-vedolizumab antibodies (AVA) analysis.
26. Replaced the existing Contraception and Pregnancy Avoidance language with 4 new subsections containing updated language for contraception and pregnancy avoidance, and clarified in Appendix C that highly effective contraception must be used.
27. Clarified the pregnancy form requirement for female partners of male subjects.
28. Added a requirement to document missed doses of antibiotic companion medication.
29. Changed wording in the safety section from *severity* to *intensity*.
30. Added frequency to list of pretreatment event and adverse event reporting.
31. Clarified that AVA titers are analyzed.
32. Clarified that the subject diary for Crohn's Disease Activity Index is electronic.
33. Clarified when serum versus urine pregnancy testing done.
34. Clarified that pregnancy testing is performed before study drug dosing at dosing visits.
35. Added an investigator responsibility per updated International Conference on Harmonisation guideline.

INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc.
Takeda Development Centre Europe, Ltd.</td><td colspan="2">Compound:
Vedolizumab IV</td></tr>
<tr><td colspan="2">Title of Protocol: A Randomized Double-Blind Phase 4 Study to Evaluate the Safety and Proportion of Subjects With Fistula Healing in 2 Dose Regimens of Entyvio (Vedolizumab IV) in the Treatment of Fistulizing Crohn's Disease (ENTERPRISE)</td><td>IND No.:
009125</td><td>EudraCT No.:
2015-000852-12</td></tr>
<tr><td colspan="2">Study Number: Vedolizumab-4003</td><td colspan="2">Phase: 4</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 4, randomized, double-blind, multicenter study to evaluate the safety and the proportion of subjects with fistula healing in 2 dose regimens of Entyvio (vedolizumab IV) over a 30-week treatment period (with the last dose at Week 22). Approximately 100 subjects with moderately to severely active Crohn's disease (CD) with 1 to 3 draining perianal fistula(e) will be enrolled. Subjects must have historically had an inadequate response with, lost response to, or been intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF-α) antagonist for their underlying CD to be eligible. Subjects will be followed for approximately 52 weeks, including screening and post-study telephone follow-up.</td></tr>
<tr><td colspan="4">Primary Objectives:
To evaluate the proportion of subjects with perianal fistula healing at Week 30 with 2 different dose regimens of vedolizumab IV 300 mg in subjects with fistulizing CD.</td></tr>
<tr><td colspan="4">Secondary Objective:
To evaluate fistula healing over a 30-week evaluation period.
Additional Objectives:
• To evaluate magnetic resonance imaging (MRI) assessment of fistula healing at Week 30 compared to Screening.
• To evaluate clinical disease activity assessed by Perianal Disease Activity Index (PDAI) and Crohn's Disease Activity Index (CDAI) from Day 1 to Weeks 2, 6, 10, 14, 22, and 30.
• To evaluate perianal pain at Week 30 compared to Day 1.
• To explore biomarkers (fecal calprotectin and C-reactive protein [CRP]) at Week 30 compared to Day 1.
• To evaluate quality of life measures (Inflammatory Bowl Disease Questionnaire [IBDQ] and EuroQol-5 dimensions [EQ-5D]) at Weeks 14 and 30 compared to Day 1.
• To assess perianal fistula draining by number of pads used at Week 30 compared to Baseline (at selected study sites).
• To evaluate pharmacokinetics of vedolizumab in CD subjects with fistula(e) over 30-week treatment period.
• To assess immunogenicity of vedolizumab over 40 weeks of follow-up.
Safety Objective:
The safety objective is to assess safety of vedolizumab IV in CD subjects with fistula(e) over 40 weeks of follow-up.</td></tr>
<tr><td colspan="4">Subject Population: Adult subjects, aged 18 to 80 years, inclusive, with moderately to severely active CD and 1 to 3 draining perianal fistula(e) of at least 2 weeks duration.</td></tr>
<tr><td colspan="2">Number of Subjects:
Approximately 100 Subjects</td><td colspan="2">Number of Sites:
Approximately 40 sites in North America and Europe</td></tr>
</table>

Dose Level(s):	**Route of Administration:**
Group 1: Vedolizumab IV 300 mg dose at Weeks 0, 2, 6, 14 and 22, and a placebo infusion at Week 10. **Group 2**: Vedolizumab IV 300 mg dose at Weeks 0, 2, 6, 10, 14 and 22.	Intravenous (IV)
Duration of Treatment:	**Period of Evaluation:**
30-week Treatment Period (with last dose at Week 22)	The study includes a 4-week Screening Period, a 30-week Treatment Period (with last dose at Week 22), and an 18-week Follow-up Period following last dose. The duration of the study from Screening to 18 weeks post last dose at Week 22 will be approximately 44 weeks**.** All subjects will participate in a long-term, follow-up (LTFU) safety survey by telephone 6 months after their last dose.

Main Criteria for Inclusion:

Adult subjects, aged 18 to 80 years, inclusive, with moderately to severely active CD and 1 to 3 draining perianal fistula(e) of at least 2 weeks duration.

Subjects who have historically had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist for their underlying CD (does not require treatment failure for currently active draining fistula); for subjects from France only: subjects who have historically failed (ie, had an inadequate response with, lost response to, or was intolerant to) infliximab for treatment of their underlying CD or fistulizing CD.

Main Criteria for Exclusion:

Subjects who have perianal abscesses greater than 2 cm or an abscess that the investigator feels requires drainage based on either clinical assessment or MRI.

Subjects who have a CDAI score greater than 400.

Subjects who have ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.

Subjects who have significant anal or rectal stenosis.

Subjects who have any evidence of an active infection (eg, sepsis, cytomegalovirus, or listeriosis) during Screening other than related to the fistula(e).

Subjects who have a positive progressive multifocal leukoencephalopathy (PML) subjective checklist.

Subjects who have received any investigational or approved biologic or biosimilar agent within 60 days of randomization.

Subjects who have had prior exposure to vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) therapy.

Subjects who have active or latent tuberculosis.

Subjects who have a known history of hepatitis B virus (HBV), hepatitis C virus (HCV), acquired human immunodeficiency virus (HIV), or are found to be seropositive at Screening.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is the proportion of subjects with a reduction of at least 50% from Day 1 in number of draining perianal fistulae at Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

Secondary endpoints for this study are:

- The proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining perianal fistulae at both Week 22 and Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

- The proportion of subjects with 100% perianal fistulae closure at Week 30 (where all fistulae are no longer draining despite gentle finger compression).
- Time to first perianal fistula closure.
- Time to last (100%) perianal fistulae closure.
- Duration of perianal fistula response (eg, number of days with drainage).

Additional endpoints for this study are:

- Proportion of subjects with reduction of fluid collections/abscess (reduction in relative mean T2 intensity on MRI) at Week 30 compared to Screening.
- Percentage reduction in relative mean T2 intensity on MRI at Week 30 compared to Screening.
- Change in Van Assche total MRI score at Week 30 compared to Screening.
- Change in individual MRI descriptors from post-contrast enhanced T1-weighted images at Week 30 compared to Screening.
- Changes in PDAI scores from Day 1 to Weeks 2, 6, 10, 14, 22 and 30.
- Changes in CDAI scores from Day 1 to Weeks 2, 6, 10, 14, 22 and 30, for subset with CDAI >220 at Day 1.
- Proportion of subjects with ≥30% decrease in mean perianal pain as assessed by Likert scale for the 7 days prior to Week 30 compared to the 7 days prior to Day 1.
- Change in biomarkers (fecal calprotectin and CRP) at Week 30 compared to Day 1.
- Change in IBDQ total and subscale scores from Day 1 to Weeks 14 and 30.
- Change in the EQ-5D utility score and visual analog scale from Day 1 to Weeks 14 and 30.
- Change in number of pads used for perianal fistula drainage from Baseline to Week 30 (selected study sites only).
- Trough concentrations of vedolizumab.
- Proportion of subjects with positive anti-vedolizumab antibodies (AVAs) and neutralizing AVAs.

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), serious adverse events (SAEs), vital signs, and results of standard laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis).

Statistical Considerations: For all dichotomous endpoints, corresponding rates and a 95% confidence intervals (CIs) will be reported by treatment group. The rate differences between treatment groups and their 95% CIs will also be reported.

Time to first fistula closure and time to last fistula closure will be analyzed by survival analysis procedures. Fistula closure rates from the time of randomization to the end of the study period will be estimated by Kaplan-Meier product limit methods and presented with appropriate 95% CIs.

Other endpoints will be summarized descriptively by treatment group.

Sample Size Justification:

A sample size of 100 subjects (50 per group) will generate 95% CIs for fistulae closure rates for each treatment group with half widths no wider than 13.9%; in addition, the 95% CIs for the difference in fistulae closure rates between the 2 groups will be no wider than 19.6%. The sample size calculation was not based on statistical power considerations but on estimates of precision.

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 document. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, 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
6-MP	6-mercaptopurine
ACCENT II	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVA	anti-vedolizumab antibody
BID	twice daily
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CRA	clinical research assistant
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
C_{trough}	trough serum concentration
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENTYVIO	vedolizumab IV
EQ-5D	Euro Quality of Life-5D
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hCG	human chorionic gonadotropin
HRQOL	health-related quality of life
IAC	Independent Adjudication Committee
IAG	Image Acquisition Guidelines
IB	Investigator's Brochure

IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
IV	intravenous(ly)
JCV	John Cunningham virus
LFT	liver function tests
LTFU	long-term follow-up
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
Med ID	medication identification number
MRI	magnetic resonance image
nAVA	neutralizing anti-vedolizumab antibodies
NSAID	nonsteroidal anti-inflammatory drug
PDAI	Perianal Disease Activity Index
PD	pharmacodynamics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	orally
PP	per protocol
PTE	pretreatment event
Q4W	once every 4 weeks
Q8W	once every 8 weeks
QD	once daily
QuantiFERON	test for mycobacterium tuberculosis
RAMP	Risk Assessment and Minimization for PML
RF	radiofrequency
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Information
SUSAR	suspected unexpected serious adverse reaction
T1	T1 weighted MRI image
T2	T2 weighted MRI image
TB	tuberculosis

TID	3 times daily
TNF-α	tumor necrosis factor-alpha
TYSABRI	natalizumab
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
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease and Current Treatments

Inflammatory bowel disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal (GI) tract that includes 2 entities, namely ulcerative colitis (UC) and Crohn's disease (CD). In contrast to the diffuse, superficial, continuous inflammation limited to the colon in UC, the inflammation of CD is focal, may be transmural, and can involve any segment of the GI tract from mouth to anus. The prevalence of CD is approximately 150/100,000 of the United States (US) population and approximately 125/100,000 of population in Western Europe [1-3]. The characteristic pathology involves a chronic inflammatory infiltrate consisting of neutrophils and macrophages. Hallmarks of CD include granulomatous inflammation and aphthous ulceration.

CD is neither medically or surgically curable at the current time. Fistulizing disease complicates CD in up to 40% of patients [4,5]. Patients with fistulizing CD experience symptoms of anal pain, purulent discharge, and incontinence, which result in high morbidity and impaired quality of life [6,7].

Fistulae rarely heal spontaneously and usually require medical therapy or surgery. Although a range of medical and surgical options is available for CD, effective treatment options for fistulizing disease are limited. There is no demonstrated role for aminosalicylates or corticosteroids in perianal CD [8]. While antibiotics may contribute to healing, they are recommended as adjunctive therapy for fistulae [8]. Thiopurines may have a moderate effect in treating fistulizing CD, however the data are limited or mixed [8-10]. Infliximab, a tumor necrosis factor-alpha (TNF-a) antagonist monoclonal antibody, has been shown to be effective in fistula healing in 2 prospective randomized controlled trials [11,12]. A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients with Fistulizing Crohn's Disease (Accent II) study reported that 36% of patients who responded to induction therapy and received maintenance infliximab therapy maintained complete fistula closure compared with 19% receiving placebo (p=0.009) [13]. Infliximab has approved indications in fistulizing CD by both the US and European regulatory agencies. Other TNF-a antagonist therapies (eg adalimumab, certolizumab) have post hoc subgroup analyses and limited prospective data dedicated to fistulizing CD [14-16].

The management of perianal CD is challenging and often requires a comprehensive approach including medical and surgical interventions. The recent global consensus guidelines on fistulizing CD contain algorithms including medical therapy +/- surgical seton [8,17], and a recent meta-analysis suggests an advantage of combination of medical and surgical therapy compared to either therapy alone [18].

4.1.2 Vedolizumab

Vedolizumab (also called MLN0002) is a humanized immunoglobulin (Ig) G1 monoclonal antibody (mAb) directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$integrin mediates

lymphocyte trafficking to the GI mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [19-22]. Vedolizumab binds the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing lymphocytes into gastrointestinal mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [23].

Vedolizumab IV (also known as ENTYVIO; KYNTELES; or MLN0002 IV) has been granted marketing approval in several regions, including the United States and European Union. Vedolizumab IV is approved for the treatment of adult patients with moderately to severely active UC and CD, who have failed conventional treatment, such as immunomodulators, corticosteroids, or TNF-α antagonists. The approved dosing and administration regimen is 300 mg vedolizumab IV infused intravenously 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 in healthy subjects and subjects with UC or CD.

4.1.2.1 Nonclinical

No nonclinical studies have been conducted to evaluate vedolizumab specifically for fistulizing CD.

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

4.1.2.2 Human Experience

In the clinical development program, more than 4200 subjects have received at least 1 dose of vedolizumab (see Investigator's Brochure [IB], Edition 19). Phase 3 placebo-controlled studies enrolled 2427 subjects with UC or CD, of whom 1434 subjects were administered 300 mg of vedolizumab for induction followed by once every 4 weeks (Q4W) or Q8W for up to a total of 52 weeks and 488 subjects were administered 300 mg vedolizumab for induction only [24,25] [26].

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 300 mg infusion at Weeks 0 and 2 (induction) followed by administration Q4W or Q8W from Weeks 6 through 52 (maintenance) demonstrated statistically significant differences in efficacy compared to placebo for both the induction and maintenance phases. The study met its primary endpoint for the induction phase, clinical remission at Week 6, but did not meet the second primary endpoint of enhanced clinical response (Crohn's Disease Activity Index [CDAI]-100) at Week 6 in the overall

population, although the treatment difference favored vedolizumab. The study did meet its primary endpoint for the maintenance phase, clinical remission at Week 52, as well as important secondary endpoints, including enhanced clinical response at Week 52 and corticosteroid-free clinical remission at Week 52 [25].

In Study C13007, 37% of subjects had a history of fistulizing disease and 15% had active draining fistulae at Baseline (Week 0) [25]. The majority of fistulae were located perianally (72% placebo; 82% vedolizumab group). At Week 52, 41.2% of subjects administered vedolizumab Q8W and 22.7% of subjects administered vedolizumab Q4W compared to 11.1% of placebo subjects achieved complete closure of baseline draining fistulae [27]. In a post hoc, exploratory analysis of the subpopulation with baseline draining fistula, 28% of subjects who received vedolizumab (combined Q4W and Q8W) had closure at Week 14 compared with 11% of subjects who received placebo. Kaplan-Meier probability estimates of fistula closure with vedolizumab were 29% and 33% at 6 and 12 months, respectively; notably, the number of subjects at risk was small. The hazard ratio for fistula closure for the vedolizumab treatment group was 2.54 (95% confidence interval [CI], 0.54-11.96) [28].

Vedolizumab has shown an acceptable and consistent safety profile in clinical trials (see current version of IB). In the pivotal phase 3 studies (C13006 in UC and C13007 in CD), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (SAEs) have been related to exacerbations or complications of the underlying UC or CD. For those infections that were reported more frequently in vedolizumab-treated subjects, the sites of these infections correlated with the known tissue distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). A total of 4% of vedolizumab-treated subjects and 3% of placebo-treated subjects experienced an infusion-related reaction. In C13006 and C13007, 10% of subjects were positive for 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 C13008, a long-term safety study, is consistent with safety in the completed studies.

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

Overall, vedolizumab was well tolerated in clinical studies. For additional safety related information from the clinical trial experience, see the current edition of the IB.

4.2 Rationale for the Proposed Study

The treatment of fistulizing CD is challenging and there are limitations in the available CD literature, which further complicates an evidence-based approach to treatment. Well-designed prospective clinical trials specific to the fistulizing CD patient population are needed.

The current study will generate meaningful data with vedolizumab IV in the treatment of perianal fistula(e) and is expected to provide guidance on an optimal dose regimen for this complex patient population.

The study will evaluate perianal fistula(e) healing rates in 2 vedolizumab treatment arms: the standard dosage regimen and the standard dosage regimen plus an additional Week 10 dose. It is postulated that addition of a Week 10 dose may be beneficial based on data from nonresponders at Week 6 that continued Q4W dosing in the C13007 study, where it was suggested that subjects who do not respond by Week 6 should be given an additional dose at Week 10. Week 10 dosing is an approved dose regimen for the treatment of CD in the European Union. The study hypothesis is that both treatment arms will be efficacious and safe for the treatment of perianal fistula(e) in subjects with CD with or without setons, and the intention is to estimate perianal fistula healing rates at Week 30 in both treatment arms, although no formal comparison between the groups will be performed.

4.3 Benefit:Risk Assessment

Perianal fistulae are a debilitating complication of CD. The treatment approach is challenging and therapeutic outcome is often insufficient or has limitations. Results from Study C13007 showed that treatment with vedolizumab IV 300 mg Q8W or Q4W maintained remission in the broad CD population and achieved fistula closure in a subpopulation of subjects who had draining fistulae at Baseline.

Study Vedolizumab-4003 is designed to investigate vedolizumab IV in the treatment of perianal fistulae and is expected to provide guidance on an optimal dosing regimen for this complex patient population. The study will evaluate perianal fistula healing rates in 2 vedolizumab treatment arms: the standard dosage regimen and the standard dosage regimen plus an additional Week 10 dose. Week 10 dosing is an approved dose regimen for the treatment of CD in the European Union (EU). The study hypothesis is that both treatment arms will be efficacious and safe for the treatment of perianal fistula in subjects with CD, and the intention is to estimate perianal fistula healing rates at Week 30 in both treatment arms, although no formal comparison between the groups will be performed. Diagnostic procedures to be used in this study (eg, MRI) are commonly used in medical practice and in this patient population.

The dosing and administration regimen are consistent with the approved vedolizumab IV label in the EU [29]. The proposed protocol will include safety measures similar to those conducted in the vedolizumab IV UC and CD clinical programs, including sufficient safety measures, evaluations, and discontinuation criteria to assure safety in the individual subjects in the planned study.

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

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to evaluate the proportion of subjects with perianal fistula healing at Week 30 in 2 different dose regimens of vedolizumab IV 300 mg in subjects with fistulizing CD.

5.1.2 Secondary Objective

The secondary objective is to evaluate fistula healing over a 30-week evaluation period.

5.1.3 Additional Objectives

Additional objectives include:

- To evaluate magnetic resonance imaging (MRI) assessment of fistula healing at Week 30 compared to Screening.
- To evaluate clinical disease activity assessed by Perianal Disease Activity Index (PDAI) and CDAI from Day 1 to Weeks 2, 6, 10, 14, 22 and 30.
- To evaluate perianal pain using a Likert scale at Week 30 compared to Day 1.
- To explore biomarkers of disease activity (fecal calprotectin and C-reactive protein [CRP]) at Week 30 compared to Day 1.
- To evaluate quality of life measures (inflammatory bowel disease questionnaire [IBDQ] and Euro Quality of Life-5D [EQ-5D]) at Week 14 and Week 30 compared to Day 1.
- To assess perianal fistula draining by number of pads used at Week 30 compared to Baseline (selected study sites only).
- To evaluate the PK of vedolizumab in CD subjects with fistula(e) over the treatment period.
- To assess immunogenicity of vedolizumab over 40 weeks of follow-up.

5.1.4 Safety Objective

- To assess safety of vedolizumab IV in CD subjects with fistula(e) over 40 weeks of follow-up.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint for this study is the proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining perianal fistulae at Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

5.2.2 Secondary Endpoints

Secondary endpoints are as follows:

- The proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining perianal fistulae at both Week 22 and Week 30 (where closed fistulae are no longer draining despite gentle finger compression).
- The proportion of subjects with 100% perianal fistulae closure at Week 30 (where all fistulae are no longer draining despite gentle finger compression).
- Time to first perianal fistula closure.
- Time to last (100%) perianal fistulae closure.
- Duration of perianal fistula response (number of days with drainage).

5.2.3 Additional Endpoints

Additional endpoints include the following:

- Proportion of subjects with reduction of fluid collections/abscess (reduction in relative mean T2 intensity on MRI) at Week 30 compared to Screening.
- Percentage reduction in relative mean T2 intensity on MRI at Week 30 compared to Screening.
- Change in Van Assche total MRI score at Week 30 compared to Screening.
- Change in individual MRI descriptors from post-contrast enhanced T1-weighted images at Week 30 compared to Screening.
- Changes in PDAI scores from Day 1 to Weeks 2, 6, 10, 14, 22 and 30.
- Changes in CDAI scores from Day 1 to Weeks 2, 6, 10, 14, 22 and 30, for subset with CDAI >220 at Day 1.
- Proportion of subjects with ≥30% decrease in mean perianal pain as assessed by Likert scale for the 7 days prior to Week 30 compared to the 7 days prior to Day 1.
- Change in biomarkers (fecal calprotectin and CRP) at Week 30 compared to Day 1.
- Change in IBDQ total and subscale scores from Day 1 to Weeks 14 and 30.
- Change in the EQ-5D utility score and visual analog scale from Day 1 to Weeks 14 and 30.
- Change in number of pads used for perianal fistula drainage from Baseline to Week 30 (selected study sites only).
- Trough serum concentrations (C_{trough}) of vedolizumab.
- Proportion of subjects with positive (AVAs), and neutralizing anti-vedolizumab antibodies (nAVAs).

5.2.4 Safety Endpoints

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), SAEs, vital signs, and results of standard laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 4, randomized, double-blind, multicenter study to evaluate the safety and the proportion of subjects with fistula healing in 2 dose regimens of vedolizumab IV 300 mg, administered as a 30-minute infusion, over a 30-week treatment period (with the last dose at Week 22) in the healing of draining perianal fistulae in subjects with active CD. Subjects in both treatment groups entering the study may have had surgical seton placement as standard of care prior to enrollment in the study.

Approximately 100 CD subjects with moderately to severely active CD and 1 to 3 draining perianal fistula(e) of at least 2 weeks duration will be included. To be eligible, subjects must have historically had an inadequate response with, lost response to, or been intolerant to either conventional therapy or a TNF-α antagonist for their underlying CD; for subjects from France only: subjects must have historically failed (ie, had an inadequate response with, lost response to, or was intolerant to) infliximab for treatment of their underlying CD or fistulizing CD. Subjects will be randomized in a 1:1 ratio into 1 of 2 treatment groups:

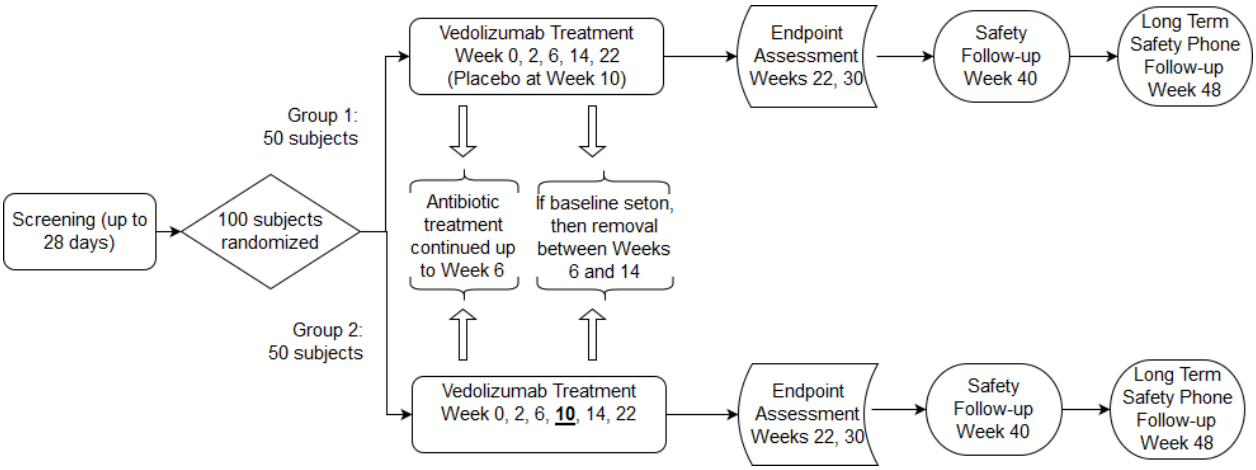
- Group 1: vedolizumab IV 300 mg dose at Week 0, 2, 6, 14, 22 and a placebo IV dose at Week 10.
- Group 2: vedolizumab IV 300 mg dose at Week 0, 2, 6, 10, 14, and 22.

The study consists of a 4-week Screening Period, a 30-week Treatment Period (with last dose at Week 22), and an 18-week Follow-up Period following the last dose. The duration of the study from Screening to 18 weeks post last dose at Week 22 will be approximately 44 weeks for all subjects. All subjects in the study will also be required to complete a long-term follow-up (LTFU) safety survey by telephone 6 months following the last dose. The end of trial will be the date of the last visit of the last subject at the Week 40 Follow-up Visit.

In both groups, for subjects with a seton at study entry, setons may be removed at or after Week 6 at the discretion of the investigator, provided that significant reduction in fistula drainage has occurred. All setons must be removed by Week 14.

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

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

Perianal fistulae are a debilitating complication of CD. The treatment approach is challenging and therapeutic outcome is often insufficient or has limitations [30]. Results from the maintenance study C13007 showed that treatment with vedolizumab IV 300 mg Q8W or Q4W maintained remission in the broad CD population and achieved fistula(e) closure in a subpopulation of subjects who had draining fistula(e) at Baseline.

The objective of this study is to prospectively evaluate vedolizumab IV in the treatment of fistulizing CD using 2 dose regimens. All subjects who meet the eligibility criteria will randomly be assigned to 1 of the 2 treatment groups. The choice of different active treatment groups, rather than a placebo comparator group was made due to ethical considerations. MRI, read by a central reader, will be used to ensure consistent classification of perianal fistulae as per Parks' criteria for classification as simple or complex fistulae [31], for scoring using the Van Assche MRI score [32], and to objectively measure perianal fistulae healing by reduction in T2 hyperintensity from Baseline and assess change in inflammatory process from Baseline on post-contrast enhanced T1-weighted images.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for vedolizumab, 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.
- At the futility analysis, if the probability of success does not meet the predetermined futility threshold and the study is stopped for futility at this point.

6.3.2 Criteria for Premature Termination or Suspension of Study 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 Study 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 study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study 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. In the case of subject screen failure, the subject may be considered for rescreening on a case-by-case basis but only with the consultation of the medical monitor.

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 has signed and dated a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is male or female and aged 18 to 80 years, inclusive.
4. The subject has a diagnosis of CD established at least 3 months prior to randomization by clinical and endoscopic evidence and corroborated by a histopathology report.
5. The subject has a diagnosis of a minimum of 1 perianal draining fistula of at least 2 weeks duration as a complication of moderately to severely active CD, as identified on MRI at Screening. Other types of fistulae (enterocutaneous, abdominal) except rectovaginal fistulae are permitted, but the number of draining perianal fistulae is limited to 3.
6. *All countries except France:* The subject, historically, had an inadequate response with, lost response to, or was intolerant to either conventional therapy or a TNF-α antagonist for their underlying CD (does not require treatment failure for currently active draining fistula).

   France only: The subject, historically, failed (ie, had an inadequate response with, lost response to, or was intolerant to) infliximab for treatment of their underlying CD or fistulizing CD.
7. If the subject had noncutting perianal seton placement as part of standard care, seton must be removed by Week 14 of the study.
8. The subject is willing and able to undergo MRI per protocol requirements.
9. The subject is willing and able to take antibiotic treatment (metronidazole, ciprofloxacin, amoxicillin clavulanate, or tinidazole, as per local label) from Day 1 through study Week 6.
10. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use a barrier method of contraception (eg, condom with spermicide)* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose. The female partner of a male subject should also be advised to use a highly effective method of contraception*.

11. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

    *Definitions and highly effective methods of contraception are defined in Section 9.1.25 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.26 Pregnancy.

12. Subjects with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factors must be up-to-date on colorectal cancer surveillance (may be performed during Screening as standard of care).

7.2 Exclusion Criteria

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

1. The subject has a diagnosis of ulcerative colitis or indeterminate colitis.
2. The subject has a perianal abscess greater than 2 cm or an abscess that the investigator feels requires drainage based on either clinical assessment or MRI. (Note: if subject has an abscess larger than 2 cm, and abscess is drained and seton placed, then subject may be rescreened with consultation from the medical monitor).
3. The subject has a CDAI score >400.
4. The subject has an ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.
5. The subject has significant anal or rectal stenosis.
6. The subject has active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:
    a. A diagnostic TB test performed during Screening that is positive, as defined by:
        i. A positive test for tuberculosis (QuantiFERON) or 2 successive indeterminate QuantiFERON tests ***OR***
        ii. A tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone)
    b. Chest X-ray within 3 months prior to Day 1, that is suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON tests within 30 days prior to Screening or during the Screening Period.

    Note: if the subject has a documented negative diagnostic TB test in the previous 3 months, screening testing does not need to be repeated provided subject has no risk factors for exposure.
7. The subject has chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection** or a known history of human immunodeficiency virus (HIV) infection

(or is found to be seropositive at Screening) or subject is immunodeficient (eg, due to organ transplantation, history of common variable immunodeficiency).

* Subjects who are positive for hepatitis B virus 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 the subject is HCV antibody positive, then a viral load test will be performed. If the viral load test is positive, then the subject will be excluded.

8. The subject has evidence of active *C. difficile* infection or is having treatment for *C. difficile* infection or other intestinal pathogens during Screening.
9. The subject has evidence of an active infection (eg, sepsis, cytomegalovirus, or listeriosis) during Screening, other than related to the fistula(e).
10. The subject currently requires or has a planned surgical intervention for CD during the study.
11. The subject has a contraindication for MRI. See MRI Image Acquisition Guidelines (IAG) for additional information.
12. The subject has allergies to and/or contraindications for metronidazole and ciprofloxacin and amoxicillin clavulanate and tinidazole (including interacting drugs such as tizanidine).
13. In the opinion of the investigator, the subject is likely to require greater than 6 weeks of treatment after Day 1 with metronidazole, ciprofloxacin, amoxicillin clavulanate, or tinidazole for the treatment of abscess.
14. The subject is taking, has taken, or is required to take any excluded medications (as listed in Section 7.3).
15. The subject has received non-biologic investigational therapy within 30 days prior to randomization.
16. The subject has received an approved non-biologic therapy (including 5-aminosalicylate [5-ASA], corticosteroid, azathioprine, 6-mercaptopurine [6-MP], etc.) in an investigational protocol within 30 days prior to randomization.
17. The subject has received any investigational or approved biologic or biosimilar agent within 60 days of randomization.
18. The subject has a history of hypersensitivity or allergies to vedolizumab or its components.
19. The subject has any prior exposure to vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or anti-MAdCAM-1 therapy.
20. The subject has received any live vaccinations within 30 days prior to randomization.
21. The subject has current rectovaginal fistula.
22. The subject currently has more than 3 draining perianal fistulae.

23. The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist at Screening or Day 1 visit.
24. The subject has a history of malignancy, except for the following: adequately-treated nonmetastatic basal cell skin cancer; squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to Screening; or history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to Screening. Subjects with a remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received, and must be discussed with the sponsor on a case-by-case basis prior to randomization.
25. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating or neurodegenerative disease.
26. The subject has conditions which, in the opinion of the investigator, may interfere with the subject's ability to comply with the study procedures.
27. The subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
28. The subject has any of the following laboratory abnormalities during the Screening Period:
    i. Hemoglobin level <8 g/dL.
    ii. White blood cell (WBC) count $<3 \times 10^9$/L.
    iii. Lymphocyte count $<0.5 \times 10^9$/L.
    iv. Platelet count $<100 \times 10^9$/L or $>1200 \times 10^9$/L.
    v. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN).
    vi. Alkaline phosphatase >3 × ULN.
    vii. Serum creatinine >1.5 × ULN.

    Note: Retesting laboratory values during the screening interval may be considered with consultation from the medical monitor.
29. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after participating in this study; or intending to donate ova during such time period.
30. If male, the subject intends to donate sperm during the course of this study or for 18 weeks thereafter.

31. 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.
32. 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 Visit 1.

7.3 Excluded Medications

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

- Any treatment for CD other than those listed below in Section 7.3.1 (either approved or investigational).
- Within 30 days prior to randomization and throughout the study, any of the following for the treatment of CD:
  - Nonbiologic therapies (eg, cyclosporine, thalidomide) other than those specifically listed in Section 7.3.1.
  - A nonbiologic investigational therapy.
  - An approved nonbiologic therapy in an investigational protocol.
- Any investigational or approved biologic or biosimilar agent within 60 days or of randomization and throughout the study.
- All live vaccines within 30 days prior to randomization, throughout the study treatment period and for at least 6 months after the last dose of study drug.
- Either approved or investigational biologic agents for the treatment of non-IBD conditions, other than localized injections (eg, intraocular injections for wet macular degeneration).
- Metronidazole, ciprofloxacin, amoxicillin clavulanate, or tinidazole after Week 6. Additional courses of antibiotics may be allowed, as needed, and in consultation with the medical monitor.
- Oral corticosteroids for CD, except as described in Section 7.3.1.1.
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use. (Note: occasional use of NSAIDs 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 following medications for CD are permitted during the study:

- Oral 5-ASA compounds, probiotics (eg, Culturelle, *Saccharomyces boulardii)*, with a stable dose for at least 2 weeks prior to randomization.
- 5-ASA or corticosteroid enemas/suppositories, with a stable dose for at least 2 weeks prior to randomization.
- Oral corticosteroid therapy for CD, with mandatory tapering started by Week 4 as described in Section 7.3.1.1.
- Antidiarrheals for control of chronic diarrhea.
- Immunomodulators (methotrexate, azathioprine, 6-mercaptopurine), stable for at least 8 weeks prior to randomization.
- Antibiotics to be provided to all subjects from Day 1 through Week 6 (ciprofloxacin, metronidazole, amoxicillin clavulanate, or tinidazole, as per local label) to decrease incidence of abscess. Subjects may have been on antibiotics prior to randomization. Additional courses of antibiotics may be allowed, as needed, and in consultation with the medical monitor.

7.3.1.1 Oral Corticosteroid Dosing and Tapering

The maximum dose of oral corticosteroids for the treatment of CD that may be coadministered with vedolizumab IV is 20 mg/day prednisone or 9 mg/day budesonide (or equivalent) as long as the corticosteroid dose has been stable for at least 4 weeks prior to randomization.

It is required that subjects receiving oral corticosteroids begin a tapering regimen by Week 4. An example 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.
- Budesonide should be reduced at a rate of 3 mg every 3 weeks until discontinuation.

For patients who could not tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may have been increased up to the original dose at the start of the study (should not exceed baseline dose). In such cases, the tapering regimen must be reinitiated within 2 weeks.

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 drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.27.

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

   - Liver Function Test (LFT) Abnormalities.

     Study drug 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 9.1.20), if the following circumstances occur at any time during study drug 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-MP, or methotrexate, if applicable, should be discontinued and the dose of vedolizumab held for an absolute lymphocyte count $<0.5\times10^9$/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 $\geq0.5\times10^9$/L. If the absolute lymphocyte count remains $<0.5\times10^9$/L, study drug should be discontinued and the subject withdrawn from the study.

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

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

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 should not be recorded in the *voluntary withdrawal* category. Similarly, lack of efficacy should not be recorded in the *voluntary withdrawal* category).

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

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.26.
7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
8. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit as well as safety follow-up visits 18 and 26 weeks post-treatment. 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 Drug 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 for infusion in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study drug will be provided in a glass vial as a lyophilized solid for reconstitution using 4.8 ml of sterile water for injection and dilution in 250 mL of sterile 0.9% sodium chloride. Each vial will be packaged in an appropriately labeled single vial carton.

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

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

8.1.1.2 Companion Medication

Treatment with antibiotics is required per protocol from Day 1 until Week 6 in order to ensure adequate care of subjects with perianal abscesses/fistulae. Antibiotics (metronidazole 250 mg orally [PO] 3 times daily [TID], or ciprofloxacin 500 mg twice daily [BID], or amoxicillin clavulanate 875 mg BID, or tinidazole 500 mg once daily [QD]) must be prescribed by the investigator as per the local label to decrease incidence of abscess.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study 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). A daily temperature log of the drug storage area must be maintained.

8.1.3 Dose and Regimen

The vedolizumab IV dose and regimen for both randomized groups is provided in Table 8.a. The infusion will be administered intravenously over 30 minutes. Instructions for reconstitution and blinded administration will be provided in the pharmacy manual. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion.

All subjects must also be prescribed companion antibiotic medication (metronidazole 250 mg PO TID, ciprofloxacin 500 mg PO BID, amoxicillin clavulanate 875 mg BID, or tinidazole 500 mg QD) from Day 1 until Week 6.

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description
1	300 mg IV	IV infusion with vedolizumab at Weeks 0, 2, 6, 14, 22
		IV infusion with placebo at Week 10
2	300 mg IV	IV infusion with vedolizumab at Weeks 0, 2, 6, 10, 14, 22

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study 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 eCRF(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 Study Drug Assignment and Dispensing Procedures

The investigator or the investigator's designee will access the interactive web response system (IWRS) at Screening to obtain the study-specific subject identification number (subject number). 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. At drug-dispensing visits, the investigator or designee will again contact the IWRS to register the visits.

At Weeks 0, 2, 6, 14, and 22, for all subjects in both treatment groups, a medication identification number (Med ID) will be assigned by IWRS and provided to the site by email notification. At Week 10, if the subject was randomized to the active treatment arm the Med ID number of the study drug to be dispensed will then be provided by the IWRS by email notification to the unblinded site pharmacist/nurse. At Week 10, if the subject was randomized to receive placebo at Week 10, the IWRS will provide email notification to the unblinded site/pharmacist/nurse, but no Med ID will be assigned.

To maintain the blind the IWRS will ensure the investigator or designee is unaware if a Med ID has been assigned. 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.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel. Subjects will be randomized to the 2 dose regimens of vedolizumab in a 1:1 ratio using an IWRS. Randomization will be stratified by TNF naïve versus TNF non-naïve (TNF failed) and by seton or no seton at Baseline.

8.4 Study 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. In order to maintain the blind, unblinded individuals preparing study drug will cover the product in a blinding bag prior to dispensing. All unblinded dosing information must be maintained in a secured area, accessible only by unblinded personnel, and separate from blinded information.

8.5 Unblinding Procedure

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

The investigator can perform emergency unblindings using the IWRS, if medically necessary. In all scenarios, the sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel (with the exception of the dispensing pharmacist or pharmacy personnel) are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

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

Upon receipt of sponsor-supplied drug, the designated site pharmacy 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, designated site pharmacy should acknowledge the receipt of the shipment by signing bottom half of the packing list and by recording in IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator's designated site pharmacy 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:

- Monitoring expiration dates (monitored via IWRS).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the drug accountability log is completed for the Med ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

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

The investigator's designated site pharmacy must record the current inventory of all sponsor-supplied drugs (vedolizumab IV) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed, and amount returned to the pharmacy (if applicable) 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 (by subject identifier) to whom sponsor-supplied drug is dispensed.

The investigator's designated site staff administering the study drug infusion must complete an individual subject accountability log to document if infusion was complete or if incomplete and study drug was returned to the pharmacy, including the date and amount returned to the pharmacy, including the initials, seal, or signature of the person administering the infusion. Only unblinded site personnel and unblinded clinical research assistants (CRAs) can perform drug accountability and drug returns in order to preserve blinding.

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

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

The requirements of the informed consent process are described in Section 15.2 and Appendix C.

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 through the IWRS system; 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 or age, sex, Hispanic ethnicity (as applicable), race as described by the subject, and smoking/nicotine usage 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 resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8.)

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent.

In addition, all prior biologic and/or any medication history for the treatment of CD, including date of diagnosis, with the reason for discontinuation is to be collected for subjects where possible.

9.1.3 Crohn's Disease History

CD history will include details of CD diagnosis, disease severity, surgery, hospitalizations, and extraintestinal manifestations.

9.1.4 Physical Examination Procedure

A Visit 1 (Screening) physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically

significant changes from the assessment prior to first dose examination. Additionally, abdominal mass assessment will be performed at all visits where CDAI is calculated.

9.1.5 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.

9.1.6 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, supine blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (resting more than 5 minutes).

When vital signs are scheduled at the same time as blood draws, vital signs take priority and vital signs will be taken within 5 minutes before the scheduled blood draw.

9.1.7 PML Checklist

Site staff will administer the subjective PML checklist during screening to exclude subjects with positive responses from enrolling into the study. The subjective PML checklist will be administered prior to dosing at each visit, as shown in Appendix A, to evaluate symptoms suggestive of PML. Any subjects reporting signs or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation. The symptoms from a positive PML checklist obtained after randomization will be recorded as an AE. Additional information and tools will be found in the Investigator Site File.

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 the screening or baseline examination. The condition (ie, diagnosis) should be described.

9.1.9 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. A copy of the ECG trace should be kept with the subject's notes.

9.1.10 MRI Procedure

Subjects must have safety laboratory results reviewed prior to MRI scan being performed. If a subject's serum creatinine is > 1.5 times the ULN (>1.5x ULN), the subject should not undergo the MRI procedure (see Exclusion Criteria 28).

A comprehensive description of MRI procedures is provided in the IAG and the Site Operations Manual.

MRI is the imaging modality of choice for evaluation of perianal fistulizing CD as it allows accurate localization and assessment of disease. In addition, MRI has been found to be sensitive to the degree of perianal disease activity and thereby offers an assessment of response to therapy in clinical trials.

A pelvic MRI will be performed at Screening (Visit 1) and Week 30 (Visit 8). Sites will use a 1.5T/3T Whole Body MRI scanner retrofitted with body radiofrequency (RF) coil for pelvic MRI. MRIs will be assessed by central radiologists for eligibility and scoring.

At Screening (Visit 1), the site radiologist will measure any perianal abscess for assessment of eligibility criteria (an abscess greater than 2 cm on MRI is exclusionary). Confirmation must be obtained from the central reader to confirm MRI eligibility.

An assigned central radiologist will classify fistulae using the simple and complex schema, the Parks' classification, and Van Assche score components.

Van Assche et al have developed an MRI-based scoring method for assessment of disease severity in patients with perianal fistulizing CD [32]. This objective scoring method will be used in this study for assessing response to therapy. Briefly, central radiologist will classify fistula(e) after reviewing T1- and T2-weighted images of the perianal region (pelvic MRI) which demonstrate the full extent of the perianal disease. Local inflammatory activity, an important parameter, will be assessed on T2-weighted images. Active fistulae and abscesses with active inflammatory process are visible on T2 images as hyperintense lesions due to their fluid contents, while scar tissue appears hypointense.

Relative mean T2 signal intensity changes will be assessed by comparing normalized T2 signal intensity values of inflamed perianal regions including fistula tracts to T2 signal intensity of healthy tissue (eg, muscle or fat) at follow-up time point with baseline values. In addition, post Gadolinium contrast enhanced T1-weighted imaging will be performed as part of the study MRI protocol in all subjects. Follow-up contrast-enhanced T1-weighted images will be compared to baseline images by the central reader in order to assess response to therapy.

9.1.10.1 Parks Classification

Parks described a classification system for perianal fistula [31], that will be used at Screening for classification of active fistula(e) as superficial, intersphincteric, transsphincteric, suprasphincteric, or extrasphincteric.

9.1.10.2 Van Assche MRI-Based Score

The Van Assche MRI-based score for severity of perianal CD [32] will be calculated at Screening (Visit 1) and Week 30 (Visit 8). The 6 components of the score, summarized below are summed to a total score of 0 to 24.

Number of fistula tracks	None = 0 Single, unbranched = 1 Single, branched = 2 Multiple = 3
Location	None/Not applicable = 0 Extra- or intersphincteric = 1 Transsphincteric = 2 Suprasphincteric = 3
Extension	None/Not applicable = 0 Infralevatoric = 1 Supralevatoric = 2
Hyperintensity on T2-weighted images	Absent = 0 Mild = 4 Pronounced = 8
Collections (cavities 3 mm diameter)	Absent = 0 Present = 4
Rectal wall involvement	Normal = 0 Thickened = 2

9.1.11 Fistula Draining Assessment

Fistula(e) (perianal, enterocutaneous) will be assessed for draining or closed status at each visit, as shown in Appendix A. Fistula draining assessment will preferably be performed by the same qualified designee for all assessments.

9.1.12 Primary Endpoint Measurement

The primary endpoint measure is ≥50% reduction from Day 1 in number of draining perianal fistulae at Week 30 (where closed fistulae are assessed by the investigator to be no longer draining despite gentle finger compression).

9.1.13 PDAI

The PDAI [33] includes 5 elements: the presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, the type of perianal disease, and the degree of induration. Scores range from 0 to 20, with higher scores indicating more severe disease. See Appendix E.

9.1.14 CDAI

A CDAI [34] score will be evaluated during Screening, using subject diary entries within 14 days prior to enrollment, and hematocrit results collected during Screening. A CDAI score will also be

derived at the time points specified in the Schedule of Events and at any unscheduled visit(s) due to disease exacerbation. See Appendix F. A Standard Weight Table is provided in Appendix G.

9.1.15 CDAI Diary Completion

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

9.1.16 Patient Reported Outcome Measures

Subjects will complete the IBDQ and EQ-5D health-related quality of life (HRQOL) questionnaires at the time points specified in the schedule of events (Appendix A). Subjects will also complete a Likert scale daily to assess perianal pain.

9.1.16.1 IBDQ

The IBDQ is a valid and reliable [35-37] instrument used to assess quality of life in adult subjects with IBD. It includes 32 questions on 4 domains of HRQOL: Bowel Systems (10 items), Emotional Function (12 items), Social Function (5 items), and Systemic Function (5 items). Subjects are asked to recall symptoms and quality of life from the last 2 weeks and rate each item on a 7-point Likert scale (higher scores equate to higher quality of life). A total IBDQ score is calculated by summing the scores from each domain; the total IBDQ score ranges from 32 to 224. See Appendix H.

9.1.16.2 EQ-5D Questionnaire

The EQ-5D questionnaire, developed by EuroQol, is a simple, valid and reliable [38] instrument used to measure general HRQOL in patients and includes 5 domain items - mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients choose the level of health problems they currently have on each item as “None”, “Moderate”, or “Extreme” and are scored a 1, 2, or 3, respectively. A composite EQ-5D score can be calculated from the individual scores to assess overall HRQOL. The EQ-5D visual analog scale (VAS) score is a self-assigned rating of overall health using a 20 cm visual, vertical scale, with a score of 0 as the worst and 100 as best possible health. The EQ-5D total score and EQ-5D VAS score have been shown in many studies to be valid and reliable instruments for measuring HRQOL in patients with GI diseases [39,40]. See Appendix I.

9.1.16.3 Likert Perianal Pain Scale

Subjects will complete an 11-point Likert scale as part of the subject diary to assess perianal pain, where 0 represents no perianal pain and 10 represents the worst possible perianal pain. Subjects will complete this scale every day. A mean score will be calculated for the 7 days prior to every visit. See Appendix J.

9.1.17 Pad Collection

The number of pads used daily will be collected to measure fistula drainage at selected study sites only.

9.1.18 Documentation of Concomitant Medications

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

9.1.19 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening/baseline examination. The condition (ie, diagnosis) should be described as current on the Medical History eCRF.

9.1.20 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 30 mL, and the approximate total volume of blood for the study is 166 mL. Details of these procedures, specimen handling and required safety monitoring will be given in the laboratory manual.

The clinical laboratory tests to be conducted during the study are summarized in Table 9.a.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	ALT	Bilirubin
WBC with differential (a)	Albumin	Blood
Hemoglobin	Alkaline phosphatase	Glucose
Hematocrit (b)	AST	Ketones
Platelets	Total bilirubin	Leukocyte esterase
PT/INR	Total protein	Nitrite
	Creatinine	pH
	Blood urea nitrogen	Protein
	Creatine kinase	Specific Gravity
	GGT	
	Potassium	
	Sodium	
	Calcium	
	Chloride	
	Magnesium	
	Phosphorus	
	Uric Acid	
	Glucose	

Other:
HIV
Hepatitis panel, including HBsAg and anti-HCV

Serum	Urine	Stool
CRP	hCG (for pregnancy in female subjects of childbearing potential only)	Fecal calprotectin
Pharmacokinetic samples		
AVA/nAVA		
QuantiFERON for TB		
beta hCG (for pregnancy in female subjects of childbearing potential only)		
FSH, if menopause is suspected (Screening Visit only)		

(a) WBC differential to include lymphocytes, monocytes, basophils, eosinophils, and neutrophils.
(b) Hematocrit only collected at Visits 3, 4, and 6
AVA=Anti-vedolizumab antibodies, nAVA=neutralizing anti-vedolizumab antibodies, FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, HBsAg = hepatitis B surface antigen, hCG=human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells.

The central laboratory will perform laboratory tests for hematology, serum chemistries, stool, and urinalysis. The results of safety laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

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

(Please refer to Section 7.4 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal LFTs 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 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, 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 LFTs for reporting requirements).

9.1.21 Fecal Calprotectin Sample Collection

A stool sample will be collected at Day1 and at Weeks 14 and 30 for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity.

9.1.22 Pharmacokinetic Sample Collection

Blood samples will be drawn for serum PK analysis in all subjects within 30 minutes prior to the start of infusion on Day 1, Weeks 6, 10, 14, 22, and at Week 30. One additional PK sample will be collected at Week 10 post end of infusion (as close to the end of the infusion as feasible and within 30 minutes of the end of the infusion). Serum concentrations of vedolizumab will be measured by a sandwich enzyme-linked immunosorbent assay (ELISA) assay with a validated range of 0.20 to 8.0 µg/mL.

9.1.23 Anti-Vedolizumab Antibodies Sampling

Blood samples for AVA assessment will be obtained within 30 minutes prior to dosing on Day 1, Weeks 6, 10, 14, 22, 30, and 40. All subjects will have a sample for AVA collected at Week 10 regardless of treatment group. A Week 40 follow-up AVA sample will be collected 18 weeks after the last dose of vedolizumab for subjects who do not continue on to commercial supply vedolizumab post-study (eg, last dose of vedolizumab at Week 22). A sample will be assessed for neutralizing AVA if a positive AVA is detected.

Serum titers of AVA will be determined using a validated assay. Neutralizing AVA (nAVA) will be determined on AVA positive samples using a validated assay.

Please refer to the laboratory manual for information on sample collection and preparation.

9.1.24 Tuberculosis Screening

All subjects will complete TB screening to determine eligibility, unless a negative test result is available from within 3 months prior to Screening and the subject has no risk factors for exposure. If required during screening, either a QuantiFERON test or a tuberculin skin test will be performed. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history.

9.1.25 Contraception and Pregnancy Avoidance Procedure

9.1.25.1 Male Subjects and Their Female Partners

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

9.1.25.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below).

In addition, they must be advised not to donate ova during this period.

9.1.25.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

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

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

The following procedures apply for contraception and pregnancy avoidance.

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

- Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

- Hormonal methods:
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
    - Oral.
    - Intravaginal (eg, ring).
    - Transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
    - Oral.
    - Injectable.
    - Implantable.

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm

donation as part of the study procedures. Such guidance should include a reminder of the following:

a. Contraceptive requirements of the study
b. Reasons for use of barrier methods (ie, condom) in males with pregnant partners
c. Assessment of subject compliance through questions such as
    i. Have you used the contraception consistently and correctly since the last visit?
    ii. Have you forgotten to use contraception since the last visit?
    iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?
    iv. Is there a chance you could be pregnant?

5. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine hCG pregnancy test prior to receiving each IV dosing.

9.1.25.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- Assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?
  - Is there a chance you could be pregnant?

9.1.26 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and vedolizumab 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 drug, eg, after Visit 1 or within 18 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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

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

All pregnancies in subjects, including female partners of male 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.

9.1.27 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at the Screening 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 (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other, specify.

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

9.1.28 Documentation of Randomization

Randomization will be performed through the IWRS system. 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

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

The site will also document missed doses of antibiotic companion medication.

If a subject is persistently noncompliant with the study drug, it may be appropriate to withdraw the subject from the study.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening Visit 1

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 9.1.27 for procedures for documenting screening failures.

Procedures to be completed at Screening Visit 1 can be found in the Schedule of Study Procedures (Appendix A).

9.3.2 Randomization (Day 1) (Visit 2)

Randomization will take place on Day 1. The Day 1 procedures are documented in Appendix A.

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 given infusion instructions for the first dose of study drug as described in Section 8.1.3. The procedure for documenting screening failures is provided in Section 9.1.27.

9.3.3 Week 30 or Early Termination (Visit 8)

The final treatment period visit will be performed at Week 30 (Visit 8) or at the Early Termination Visit, if applicable (see Appendix A).

For all subjects randomized, the investigator must complete the End of Study Drug and End of Study Visits eCRF pages.

9.3.4 Week 40 Follow-up (or 18 Weeks Post-Treatment)

Follow-up will begin the first day after the last dose of vedolizumab and will continue for 18 weeks. This follow-up visit will be scheduled for safety for all subjects and for AVA assessments for all subjects who stopped vedolizumab during study (ie, not for those who continue on commercial supply vedolizumab therapy post-study) as per Appendix A.

9.3.5 Post Study Long-Term Follow-Up (or 26 Weeks Post-Treatment)

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

9.3.6 Unscheduled Visits Due to Exacerbation of CD

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

- Physical examination.
- Urine pregnancy test (for females of childbearing potential).
- Clinical chemistry and hematology, if indicated.
- AVA sample.
- Concomitant mediations.
- AE/SAE assessment.

9.3.7 Post Study Care

Vedolizumab IV treatment will not be supplied 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. The subject may be continued on commercial supply of vedolizumab, at the discretion of their physician.

9.4 Biological Sample Retention and Destruction

In this study, samples for AVA analysis will be collected as described in Section 9.1.23.

The AVA samples will be stored for up to but not longer than 15 years from when the study results are reported or as required under applicable law or until consent is withdrawn. After that time, the samples will be destroyed.

The samples will be sent to a sponsor identified laboratory that will serve as a secure storage facility. The sponsor, its agents and affiliated companies will have access to the samples. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any individual results in confidence.

The samples will be labeled with a unique sample identifier. The samples and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

10.0 PRETREATMENT EVENTS (PTE) AND ADVERSE EVENTS (AE)

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 drug; 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 value), 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 or 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 drug 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 a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings 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 or ECG re-test and/or continued monitoring of an abnormal finding 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 medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. 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 medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. 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 drug, 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 drug, 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 intensity of AEs /Serious PTEs:

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

Preplanned procedures (surgeries or interventions):

- 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 recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

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

10.1.5 AEs of Special Interest

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

AESIs for this compound are serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or systemic reactions and hypersensitivity, as described in further detail below.

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.

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

Subjects and caregivers will be instructed to report the development of rash, hives, pruritus, flushing, urticaria, injection site pain, redness and/or swelling, etc. that may represent an

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

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

Serious Infections

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

Malignancy

All cases of malignancies that are detected during the study will be reported as AEs. Local medical practices for the management of 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 11.1.1, respectively.

10.1.6 Intensity 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 drug(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, and the time, if available.

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, and the time, if available.

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 Drug

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

10.1.13 Outcome

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Start of PTE collection:

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Day 1; Visit 2) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Start of AE collection:

AEs must be collected from the time that the subject is first administered study drug (Day 1; Visit 2). Any drugs provided by the sponsor are considered study drugs, including placebo.

End of AE collection:

Routine collection of AEs will continue until the end of study follow-up (Week 40; Visit 9).

10.2.1.2 PTE and AE Reporting

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

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

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

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

10.2.1.3 Special Interest AE Reporting

If an AESI, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria in Section 10.1.5, it should be recorded in a special interest AE eCRF or SAE Form. The applicable form should be completed and reported to the SAE reporting contact in Section 1.1 within 24 hours.

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

10.2.2 Collection and Reporting of SAEs

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

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

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

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

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

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

10.2.3 Reporting of Abnormal LFTs

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

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.20 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and

fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

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

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

11.0 STUDY-SPECIFIC COMMITTEES

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

11.1 Adjudication Committee

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

11.1.1 Risk Assessment and Minimization for PML (RAMP) Program

Natalizumab (TYSABRI), another integrin receptor antagonist, has been associated with PML, a rare and often fatal opportunistic infection of the central nervous system. PML is caused by the John Cunningham virus (JCV) and typically only occurs in patients who are immunocompromised [41,42]. Natalizumab is a pan-α4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to vascular cell adhesion molecule-1 (VCAM-1) and MAdCAM-1 [43,44]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [23] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical trials with vedolizumab to date, a risk of PML cannot be ruled out.

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

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

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

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 Electronic CRFs

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

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

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

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

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

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

12.2 Record Retention

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

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

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

A blinded data review will be conducted prior to unblinding of subjects' treatment assignments. 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

All subjects who received at least 1 dose of study drug and have a post-randomization assessment of fistula healing will be included in the full analysis set (FAS). The FAS population will be used for the analysis of the proportion of subjects with fistula healing and constitutes the primary analysis population for the endpoints associated with fistula healing.

All FAS subjects who do not have any major protocol violations will be included in the per protocol (PP) population. Major protocol violations will be specified in the SAP. All decisions to exclude subjects from the PP population dataset will be made prior to the unblinding of the study. Analyses using the PP population may be provided as a sensitivity analysis.

Safety analyses will be based on the safety analysis set. All subjects who received at least 1 dose of study drug will be included in the safety analysis set.

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarized. 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 Analysis of Fistula Healing

No inferential statistical testing will be performed in this study. Instead, an estimation approach will be taken.

The primary endpoint for this study is the proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining fistulae at Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

The first secondary endpoint is the proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining perianal fistulae at both Week 22 and Week 30 (where closed fistulae are no longer draining despite gentle finger compression).

Other secondary endpoints include the proportion of subjects with 100% fistulae closure at Week 30 (where all fistulae are no longer draining despite gentle finger compression), time to first fistula closure, time to last (100%) fistula closure, and duration of fistula response (eg, number of days with drainage).

For all dichotomous endpoints (proportion of subjects a reduction of at least 50% from Screening in the number of draining fistulae at Week 30 and proportion of subjects with 100% fistulae closure at Week 30), corresponding rates and 95% CIs will be reported by treatment group. The rate differences between treatment groups and their 95% CIs will also be reported.

Time to first fistula closure and time to last fistula closure will be analyzed by survival analysis procedures. Fistula closure rates from the time of randomization to the end of the study period will be estimated by Kaplan-Meier product limit methods and presented with appropriate 95% CIs.

Other endpoints will be summarized descriptively by treatment group.

13.1.4 PK Analysis

Serum concentrations of vedolizumab will be summarized by collection time points, and by treatment group using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing.

Data might be pooled with data from other studies. The results from these analyses will not be reported in the clinical study report (CSR) and will be part of a stand-alone report.

13.1.5 Anti-vedolizumab Antibodies Analysis

The proportion of subjects with positive and titers of AVA (transient and persistent), and proportion of subjects with positive neutralizing AVA during the study will be summarized. The impact of AVA on serum concentration, safety, and efficacy will be explored.

13.1.6 Safety Analysis

Safety analyses will be based on the safety analysis set.

No formal statistical tests or inference will be performed for safety analyses. Safety data will be presented by treatment group.

The number and percentage of subjects with AEs (regardless of relationship to study drug), AEs of special interest (ie, serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or systemic reactions, and hypersensitivity), AEs leading to discontinuation, and SAEs that occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by intensity, and by relationship to study drug. If a subject

experienced more than 1 AE for a given PT, intensity is defined as the intensity of the most severe event and relationship to study drug is the relationship of the most related event.

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

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

Data from the LTFU survey will be summarized descriptively.

13.1.7 Other Analyses

Changes from Baseline to Weeks 14 and 30 in EQ-5D and IBDQ will be summarized.

13.2 Futility Analysis and Criteria for Early Termination

A futility analysis will be performed after 25 patients per treatment arm complete to Week 30. There is no intention to stop for efficacy at this point.

13.3 Determination of Sample Size

A sample size of 100 subjects (50 per group) will generate 95% CIs for fistula closure rate with a half width no wider than 13.9%; in addition, the 95% CIs for the difference in fistula closure rates between the 2 groups will be no wider than 19.6%. The sample size was not based on statistical power considerations but on an estimate of precision.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, the vedolizumab IV (Entyvio) package insert, 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/notify site once} the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives [drug/notification] no protocol activities, including screening may occur.

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

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

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 trial database or documentation via a subject 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 the monitor or the sponsor's designee, 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 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 study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the 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 all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study 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 the sponsor providing this information to callers must provide the sponsor 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 and/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 study subjects. Refer to the 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

	Screen	Treatment						Final Visit or ET	Follow-up	Post Study
Study Day/Week:	**Days -28 to -1**	**Wk0 / Day 1**	**Wk 2**	**Wk 6**	**Wk 10**	**Wk 14**	**Wk 22**	**Wk 30**	**Wk 40 (or 18 wks post-tx if ET)**	**LTFU by Telephone Wk 48 (or 26 wks post-tx if ET)**
Visit Windows (Days):			**±2**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Informed consent	X									
Assess inclusion/exclusion criteria	X	X								
Demographics /medical and medication history/ concurrent medical conditions	X									
Crohn's disease history	X									
Tuberculosis QuantiFERON or skin test	X									
Physical examination (a)	X	X	X	X	X	X	X	X		
Fistula draining assessment (b)	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
Height and weight (c)	X	X		X	X			X		
CDAI	X (d)	X (e)	X (e)	X (e)	X (e)	X (e)	X (e)	X (e)		
PDAI		X	X	X	X	X	X	X		
ECG	X									
MRI	X (f)							X (f)		
Hematology, serum chemistry	X	X			X		X	X		
Hematocrit (for CDAI scoring)			X	X		X				
HIV/Hepatitis Panel	X									
Urinalysis	X	X			X			X		
AVA (g)		X		X	X	X	X	X	X (h)	
PK (i)		X		X	X	X	X	X		
CRP (j)		X			X	X		X		
Fecal calprotectin (k)		X				X		X		

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screen	Treatment						Final Visit or ET	Follow-up	Post Study
Study Day/Week:	**Days -28 to -1**	**Wk0 / Day 1**	**Wk 2**	**Wk 6**	**Wk 10**	**Wk 14**	**Wk 22**	**Wk 30**	**Wk 40 (or 18 wks post-tx if ET)**	**Phone Wk 48 (or 26 wks post-tx if ET)**
Visit Windows (Days):			**±2**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
PML checklist	X	X (l)	X (l)	X (l)	X (l)	X (l)	X (l)	X	X	
Provide PML wallet card		X						X		
Serum Pregnancy test (m)	X							X		
Urine Pregnancy test (m)		X	X	X	X	X	X		X	
IBDQ		X				X		X		
EQ-5D		X				X		X		
Mean Likert perianal pain score (n)	X	X	X	X	X	X	X	X		
Subject diary (n)	X	X	X	X	X	X	X	X		
Review subject diary		X	X	X	X	X	X	X		
Daily # of pads used (selected sites only)	X	X	X	X	X	X	X	X		
Dosing (IV) (o)		X	X	X	X	X	X			
Antibiotic dosing		X	X	X (p)						
Seton removal (q)				[X (q)]	[X (q)]	X (q)				
Concomitant medications	X	X	X	X	X	X	X	X		
PTE assessment	X	X								
AE/SAE assessment		X	X	X	X	X	X	X	X	
Long-term follow-up safety questionnaire										X
Access IWRS to obtain subject ID	X									
Access IWRS for randomization		X								
Access IWRS to register visit	X	X	X	X	X	X	X	X		

Footnotes are on the following page.

ET=early termination, tx=treatment, wk=week.
(a) Including abdominal mass assessment for CDAI calculation.
(b) Fistula(e) (perianal, enterocutaneous) will be assessed for draining or closed status at each visit. Fistula draining assessment will preferably be performed by the same qualified designee for all assessments. At Screening and Week 30, the assessment of perianal fistula draining is for eligibility or primary endpoint assessment, respectively.
(c) Height collected only at the Screening Visit.
(d) Hematocrit results collected during Screening will be used to calculate the CDAI score to determine eligibility.
(e) CDAI score components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components.
(f) Subjects must have safety laboratory results reviewed prior to MRI scan being performed. If a subject's serum creatinine is >1.5 times the ULN (>1.5x ULN), the subject should not undergo the MRI procedure. MRI will be performed at Screening and Week 30; MRIs will be centrally read.
(g) AVA to be collected prior to dosing. If positive AVA is detected, a sample will be assessed for neutralizing AVA.
(h) The 18-week postdose AVA sample should be collected for all subjects who stopped vedolizumab during study (ie, not for those who continue on commercial supply vedolizumab therapy post-study).
(i) PK samples to be collected at predose on Day 1, Weeks 6, 10, 14 and 22 and at Week 30. One additional PK sample will be collected at Week 10 postdose (as close to the end of the infusion as feasible, and must be obtained within 30 minutes after the end of the infusion).
(j) CRP will be measured from the hematology/serum chemistry blood draw at all weeks except Week 14. Week 14 will require a separate blood draw as hematology and serum chemistry are not taken at this time.
(k) Stool sample to be collected and sent to central laboratory for evaluation of fecal calprotectin.
(l) PML checklist must be administered prior to dosing at every dosing visit.
(m) Women of childbearing potential only. Urine pregnancy testing will be conducted at the site and serum pregnancy testing will be conducted by the central laboratory. At visits with study drug dosing, testing to be performed before any study drug dosing.
(n) Subject electronic diary to be completed as per training instruction during screening interval. Subject electronic diary (CDAI and perianal pain) to be completed daily from Screening to Week 30.
(o) Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion for monitoring for potential hypersensitivity reactions.
(p) Antibiotic companion medication that was started (or continued if subject already taking antibiotics) from Day 1, must be stopped at Week 6. Additional courses of antibiotics may be allowed, as needed, and in consultation with the medical monitor.
(q) Applicable for subjects who had a seton at study enrollment. Setons may be removed at or after Week 6 at the discretion of the investigator, provided that significant reduction in fistula drainage has occurred. All setons must be removed by Week 14.

Schedule of Samples With Dosing Sequence Requirements

	Visit 1, Screening	Visit 2, Day 1	Visit 3, Wk 2	Visit 4, Wk 6	Visit 5, Wk10	Visit 6, Wk 14	Visit 7, Wk 22	Visit 8 Wk 30	Visit 9 Wk 40
PK sample		Within 30 min before dose		Within 30 min before dose	Within 30 min before dose AND Immedi-ately after infusion (within 30 minutes of end of infusion)	Within 30 min before dose	Within 30 min before dose	Anytime during visit (before any commercial supply vedolizumab dose, if applicable)	
AVA testing		Within 30 min before dose		Within 30 min before dose	Within 30 min before dose	Within 30 min before dose	Within 30 min before dose	Anytime during visit (before any commercial supply vedolizumab dose, if applicable)	(Anytime during visit [only for subjects who stopped vedolizumab during study])
Pregnancy test	Anytime during visit	Before dose	Before dose	Before dose	Before dose	Before dose	Before dose	Anytime during visit	Anytime during visit

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

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

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

Appendix C Elements of the Subject Informed Consent

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

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

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

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

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective 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 drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- 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 PDAI

Perianal Crohn's Disease Activity Index (PDAI)

Perianal disease activity

1. Discharge
   - 0 No discharge
   - 1 Minimal mucous discharge
   - 2 Moderate mucous or purulent discharge
   - 3 Substantial discharge
   - 4 Gross fecal soiling

2. Pain/restriction of activities
   - 0 No activity restriction
   - 1 Mild discomfort, no restriction
   - 2 Moderate discomfort, some limitation activities
   - 3 Marked discomfort, marked limitation
   - 4 Severe pain, severe limitation

3. Restriction of sexual activity
   - 0 No restriction sexual activity
   - 1 Slight restriction sexual activity
   - 2 Moderate limitation sexual activity
   - 3 Marked limitation sexual activity
   - 4 Unable to engage in sexual activity

4. Type of Perianal disease
   - 0 No perianal disease/skin tags
   - 1 Anal fissure or mucosal tear
   - 2 <3 Perianal fistulae
   - 3 ≥3 Perianal fistulae
   - 4 Anal sphincter ulceration or fistulae with significant undermining of skin

5. Degree of induration
   - 0 No induration
   - 1 Minimal induration
   - 2 Moderate induration
   - 3 Substantial induration
   - 4 Gross fluctuance/abscess

Total score: _____ (sum of responses 0-20)

Instructions for Perianal Crohn's Disease Activity Index (PDAI)

The PDAI is a scale which measures the current severity of Crohn's disease involving the perianal area.

Items 1 to 3 are posed directly to the patient. The patient is asked to "Please consider your perianal symptoms and not general health or other Crohn's related symptoms for the following":

When asking the question regarding perianal discharge

For item #1

Have you had any discharge from the perianal area in the past week that caused soiling of your underclothing or had to use a pad to soak up a discharge? They may be shown or read the five response options.

For item #2, when asking about pain, it should specifically relate to perianal pain.

Have you had any perianal pain and/or restriction of your activities because of pain around the perianal area in the past week? The subject may be shown or read the 5 response options.

For item #3, it should specifically relate to the perianal Crohn's disease.

Have you had any restriction of your sexual activity because of your perianal Crohn's disease in the past week? The subject may be shown or read the 5 response options.

Items 4 and 5 are to be completed by the clinician health provider after examination of the perianal area.

The PDAI score is the sum of responses for all 5 items (range 0-20); higher score indicates more severe disease and restriction. Data on the validation of the index is found in the article below:

E. J. Irvine McMaster IBD Study Group. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. J Clin Gastroenterol. 1995 Jan;20(1):27-32. PMID: 7884173.

Appendix F 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)		x 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)		x 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)		x 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		x 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		x 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		x 10	
Hematocrit (%) (a)	Males: subtract value from 47 Females: subtract value from 42		x 6	
Body Weight (b)	(1 – (Body weight/ Standard Weight)) × 100		x 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.
(a) If hematocrit subtotal <0, enter 0. (b) If body weight subtotal <-10, enter -10.

Appendix G Table for Determining Standard Body Weight (CDAI Variable)

WOMEN	
Height in cm *without shoes*	Standard Weight in Kg
148	53.1
149	53.6
150	54.1
151	54.5
152	55.0
153	55.4
154	55.9
155	56.4
156	57.0
157	57.5
158	58.1
159	58.6
160	59.1
161	59.6
162	60.2
163	60.7
164	61.3
165	61.9
166	62.4
167	62.9
168	63.4
169	63.9
170	64.5
171	65.0
172	65.5
173	66.0
174	66.6
175	67.2
176	67.7
177	68.3
178	68.8
179	69.3
180	69.8
181	70.3
182	70.9
183	71.5
184	72.1
185	72.7
186	73.4

MEN	
Height in cm *without shoes*	Standard Weight in Kg
158	62.6
159	62.9
160	63.3
161	63.7
162	64.1
163	64.6
164	65.0
165	65.5
166	66.0
167	66.6
168	67.1
169	67.6
170	68.1
171	68.7
172	69.2
173	69.7
174	70.3
175	70.8
176	71.3
177	71.9
178	72.4
179	73.0
180	73.6
181	74.3
182	74.8
183	75.5
184	76.2
185	76.9
186	77.6
187	78.2
188	78.8
189	79.6
190	80.4
191	81.0
192	81.6
193	82.2
194	82.8
195	83.4
196	84.0

Modified for height without shoes from the 1983 Metropolitan Life Insurance Ideal Weights for Height tables.

Appendix H IBDQ

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from I through 7. Please read each question carefully and circle/mark the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option. from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

Appendix I EQ-5D

EQ-5D-3L PDA version

English (USA)

Health Questionnaire
English version for the USA

On the following screens please tap the statement that best describes your health TODAY.

Your mobility TODAY
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Your self-care TODAY
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

Your usual activities TODAY (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Your pain / discomfort TODAY
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Your anxiety / depression TODAY
I am not anxious or depressed
I am moderately anxious or depressed

I am extremely anxious or depressed
We would like to know how good or bad your health is TODAY. On the next screen you will see a scale numbered 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Please tap on the scale to indicate how your health is TODAY.
The best health you can imagine The worst health you can imagine YOUR HEALTH TODAY

Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*

Appendix J Likert Scale for Perianal Pain

This 11-point Likert rating scale will be used by subjects to assess their perianal pain each day, as below. Likert scale for perianal pain will be completed as part of the subject diary.

"How would you rate your perianal pain in the last 24 hours?"

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Source: Adapted from: Likert, R. A technique for the measurement of attitudes. Archives of Psychology 1932;140:1–55.

Appendix K Detailed Description of Amendments to Text

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

Change 1: Removed the requirement for perianal seton placement as part of standard of care before randomization.

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:	The subject had noncutting perianal seton placement as part of standard care within 1 to 4 weeks prior to randomization.
Amended or new wording:	**If** ~~T~~**t**he subject had noncutting perianal seton placement as part of standard care ~~within 1 to 4 weeks prior to randomization~~**, seton must be removed by Week 14 of the study.**

Rationale for Change:

Study population modified to allow subjects with or without seton.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 4.2 Rationale for the Proposed Study.
- Section 6.1 Study Design.
- Appendix A Schedule of Study Procedures, footnote q.

Change 2: Changed the requirements for seton removal, if applicable, from 10 to 22 weeks after randomization to 6 to 14 weeks after randomization.

The primary change occurs in Section 6.1 Study Design:

Initial wording:	In both groups, setons may be removed at or after Week 10 at the discretion of the investigator, provided that significant reduction in fistula drainage has occurred. All setons are recommended to be removed by Week 14 and must be removed by Week 22.
Amended or new wording:	In both groups**, for subjects with a seton at study entry,** setons may be removed at or after Week ~~10~~**6** at the discretion of the investigator, provided that significant reduction in fistula drainage has occurred. All setons ~~are recommended to be removed by Week 14 and~~ must be removed by Week ~~22~~**14**.

Rationale for Change:

Updated the text to apply only to subjects who have a seton at study entry, as setons are no longer required in this amendment; updated the window for seton removal so they are removed earlier in the study and do not confound endpoint assessment.

Appendix A Schedule of Study Procedures also contains this change.

Change 3: Added a secondary endpoint to evaluate fistulas healed at both Week 22 and Week 30.

The primary change occurs in Section 5.2.2 Secondary Endpoints:

Added text:
- **The proportion of subjects with a reduction of at least 50% from Day 1 in the number of draining perianal fistulae at both Week 22 and Week 30 (where closed fistulae are no longer draining despite gentle finger compression).**

Rationale for Change:

New endpoint added that is considered clinically relevant

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 13.1.3 Analysis of Fistula Healing.

Change 4: Modified inclusion criterion 6 such that both France-specific and global language is presented.

The primary change occurs in Section 7.1 Inclusion Criteria:

Added text: 6. ***All countries except France:*** The subject, historically, had an inadequate response with, lost response to, or was intolerant to either conventional therapy or a TNF-α antagonist for their underlying CD (does not require treatment failure for currently active draining fistula).

France only: **The subject, historically, failed (ie, had an inadequate response with, lost response to, or was intolerant to) infliximab for treatment of their underlying CD or fistulizing CD.**

Rationale for Change:

To consolidate prior region-specific protocols into a single global protocol amendment.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Study Design.

Change 5: Modified inclusion and exclusion criteria to allow additional types of antibiotic to reduce the incidence of abscess.

The primary changes occur in Section 7.1 Inclusion Criteria and Section 7.2 Exclusion Criteria:

Initial wording:

7.1 Inclusion Criteria

…

9. The subject is willing and able to take antibiotic treatment (metronidazole or ciprofloxacin, as per local label) from Day 1 through study Week 6.

…

7.2 Exclusion Criteria

…

12. The subject has allergies to and/or contraindications for metronidazole and ciprofloxacin (including interacting drugs such as tizanidine).
13. In the opinion of the investigator, the subject is likely to require greater than 6 weeks of treatment after Day 1 with metronidazole or ciprofloxacin for the treatment of abscess.

Amended or new wording:

7.1 Inclusion Criteria

…

9. The subject is willing and able to take antibiotic treatment (metronidazole**,** ~~or~~ ciprofloxacin**, amoxicillin clavulanate, or tinidazole,** as per local label) from Day 1 through study Week 6.

…

7.2 Exclusion Criteria

…

12. The subject has allergies to and/or contraindications for metronidazole and ciprofloxacin **and amoxicillin clavulanate and tinidazole** (including interacting drugs such as tizanidine).
13. In the opinion of the investigator, the subject is likely to require greater than 6 weeks of treatment after Day 1 with metronidazole**,** ~~or~~ ciprofloxacin**, amoxicillin clavulanate, or tinidazole** for the treatment of abscess.

Rationale for Change:

To allow additional options for antibiotics (amoxicillin clavulanate 875 mg BID, or tinidazole 500 mg QD)

The following sections also contain this change:

- Section 7.3 Excluded Medications.
- Section 7.3.1 Permitted Medications and Treatments.
- Section 8.1.1.2 Companion Medication.
- Section 8.1.3 Dose and Regimen.
- Appendix A Schedule of Study Procedures.

Change 6: Modified inclusion criteria 10 and 11 per updated safety language.

The primary change occurs in Section 7.1 Inclusion Criteria:

Initial wording:

10. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.
11. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

*Definitions and acceptable methods of contraception are defined in Section 9.1.25 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.26 Pregnancy.

Amended or new wording:

10. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use ~~adequate~~**a barrier method of** contraception **(eg, condom with spermicide)*** from signing of informed consent throughout the duration of the study and for 18 weeks after last dose. **The female partner of a male subject should also be advised to use a highly effective method of contraception*.**
11. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use ~~routinely adequate~~ **a highly effective method of** contraception* from signing of informed consent throughout the duration of the study and for 18 weeks after last dose.

*Definitions and ~~acceptable~~ **highly effective** methods of contraception are defined in Section 9.1.25 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.26 Pregnancy.

Rationale for Change:

To clarify study inclusion criteria per current safety requirements.

Change 7: Modified exclusion criteria 6 and 7 per updated safety language.

The primary change occurs in Section 7.2 Exclusion Criteria:

Initial wording:

6. The subject has active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:
    a. History of TB.
    b. A diagnostic TB test performed during Screening that is positive, as defined by:
        i. A positive test for tuberculosis (QuantiFERON) or 2 successive indeterminate QuantiFERON tests ***OR***
        ii. A tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone)

    Note: if the subject has a documented negative diagnostic TB test in the previous 3 months, screening testing does not need to be repeated provided subject has no risk factors for exposure.
7. The subject has a known history of infection with human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) or is found to be seropositive at Screening.

Amended or new wording:

6. The subject has active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:
    ~~a. History of TB.~~
    a. A diagnostic TB test performed during Screening that is positive, as defined by:
        iii. A positive test for tuberculosis (QuantiFERON) or 2 successive indeterminate QuantiFERON tests ***OR***
        iv. A tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone)
    b. **Chest X-ray within 3 months prior to Day 1 that is suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON test within 30 days prior to Screening or during the Screening Period.**

    Note: if the subject has a documented negative diagnostic TB test in the previous 3 months, screening testing does not need to be repeated provided

subject has no risk factors for exposure.

7. The subject has **chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection** or** a known history of ~~infection with~~human immunodeficiency virus (HIV)**~~, hepatitis B (HBV) or hepatitis C (HCV)~~ infection (**or is found to be seropositive at Screening**) or subject is immunodeficient (eg, due to organ transplantation, history of common variable immunodeficiency).**
***Subjects who are positive for hepatitis B virus 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 the subject is HCV antibody positive, then a viral load test will be performed. If the viral load test is positive, then the subject will be excluded.**

Rationale for Change:

To clarify exclusion criteria per preferred safety wording.

Change 8: Modified exclusion criterion 17 to remove the option of 5 half lives as washout window.

The primary change occurs in Section 7.2 Exclusion Criteria:

Deleted text: 17. The subject has received any investigational or approved biologic or biosimilar agent within 60 days ~~or 5 half lives (whichever is longer)~~ of randomization.

Rationale for Change:

To clarify that 60 days is considered a sufficient washout period.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 7.3 Excluded Medications.

Change 9: Modified exclusion criterion 19 to also exclude subjects with prior exposure to etrolizumab or anti-mucosal addressin cell adhesion molecule-1 therapy therapy.

The primary change occurs in Section 7.2 Exclusion Criteria:

Initial wording: 19. The subject has any prior exposure to vedolizumab, natalizumab, efalizumab, or rituximab.

Amended or new wording: 19. The subject has any prior exposure to vedolizumab, natalizumab, efalizumab, ~~or~~ rituximab**, etrolizumab, or anti-MAdCAM-1 therapy**.

Rationale for Change:

To exclude subjects with exposures to etrolizumab or anti-MAdCAM-1 therapy

Section 2.0 STUDY SUMMARY also contain this change.

Change 10: Reduced the study sample size from 126 (63 per group) to 100 (50 per group).

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

Initial wording:	A sample size of 126 subjects (63 per group) will generate 95% CIs for fistula closure rate with a half width no wider than 12.4%; in addition, the 95% CIs for the difference in fistula closure rates between the 2 groups will be no wider than 17.6%. The sample size was not based on statistical power considerations but on an estimate of precision.
Amended or new wording:	A sample size of ~~126~~**100** subjects (~~63~~**50** per group) will generate 95% CIs for fistula closure rate with a half width no wider than ~~12.4~~**13.9** %; in addition, the 95% CIs for the difference in fistula closure rates between the 2 groups will be no wider than ~~17.6~~**19.6**%. The sample size was not based on statistical power considerations but on an estimate of precision.

Rationale for Change:

To modify the study sample size.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 6.1 Study Design.

Change 11: Increased the number of study sites from 30 to 40.

The primary change occurs in Section 2.0 STUDY SUMMARY:

Initial wording:	Approximately 30 sites in North America and Europe
Amended or new wording:	Approximately ~~30~~**40** sites in North America and Europe

Rationale for Change:

To increase study recruitment

Change 12: Added a stratification factor for seton or no seton at randomization.

The primary change occurs in Section 8.3 Randomization Code Creation and Storage:

Added text: Randomization will be stratified by TNF naïve versus TNF non-naïve (TNF failed) **and by seton or no seton at Baseline**.

Rationale for Change:

To balance groups by seton use, given that setons are no longer required as of this amendment.

Change 13: Added a futility analysis after 25 subjects complete the primary endpoint assessment (Week 30).

The primary change occurs in Section 13.2 Futility Analysis and Criteria for Early Termination:

Initial wording:	**13.2 Interim Analysis and Criteria for Early Termination** No interim analysis, nor criteria for early termination of the study are planned.
Amended or new wording:	**13.2 ~~Interim~~Futility Analysis and Criteria for Early Termination** ~~No interim analysis, nor criteria for early termination of the study are planned.~~**A futility analysis will be performed after 25 patients per treatment arm complete to Week 30. There is no intention to stop for efficacy at this point.**

Rationale for Change:

To add a futility analysis

The following sections also contain this change:

- Section 6.3.1 Criteria for Premature Termination or Suspension of Study Sites.
- Section 13.2 Futility Analysis and Criteria for Early Termination.

Change 14: Updated background information per the current Investigator's Brochure.

The primary change occurs in Section 4.1.2.2 Human Experience:

Initial wording:	In the clinical development program more than 3400 subjects have received at least 1 dose of vedolizumab (see Investigator's Brochure [IB], Edition 17).
Amended or new wording:	In the clinical development program more than ~~3400~~ **4200** subjects have received at least 1 dose of vedolizumab (see Investigator's Brochure [IB], Edition ~~17~~**19**).

Rationale for Change:

Updated per Investigator's Brochure Edition 19.

Change 15: Revised the rationale for the proposed study given that perianal seton replacement no longer required.

The primary change occurs in Section 4.2 Rationale for the Proposed Study:

Deleted text:	~~Treatment in both arms will be combined with standard of care surgical intervention (seton) based on recent literature, which suggests benefit of a combined surgical and medical approach for patients with CD perianal fistulae [8,17,45].~~

Rationale for Change:

Updated on the basis of changes to the study population as of this amendment.

Change 16: Revised the benefit-risk assessment given that perianal seton replacement no longer required.

The primary change occurs in Section 4.3 Benefit:Risk Assessment:

Deleted text:	~~Treatment in both arms will be combined with standard of care surgical intervention (seton) based on recent literature, which suggests benefit of a combined surgical and medical approach for patients with CD perianal fistulae [8,17,45]. The combination of vedolizumab therapy with surgical standard of care is intended to minimize the risk of treatment failure.~~

Rationale for Change:

Updated on the basis of changes to the study population as of this amendment.

Change 17: Modified the Schematic of Study Design given the changes in this amendment.

The primary change occurs in Figure 6.a Schematic of Study Design:

Description of Change:	• Removed standard care seton before randomization. • Modified sample size to 100 subjects randomized. • Clarified that "If baseline seton" then removal beween Weeks 6 and 14. • Added endpoint assessment at Week 22.

Rationale for Change:

Updated the figure on the basis of changes to the study design as of this amendment

Change 18: Changed the maximum dose of oral corticosteroids from 30 to 20 mg/day and clarified that tapering schedule provided is an example of one schedule; allowed for return to baseline corticosteroid dose.

The primary change occurs in Section 7.3.1.1 Oral Corticosteroid Dosing and Tapering:

Initial wording:	The maximum dose of oral corticosteroids for the treatment of CD that may be coadministered with vedolizumab IV is 30 mg/day prednisone or 9 mg/day budesonide (or equivalent) as long as the corticosteroid dose has been stable for at

	least 4 weeks prior to randomization. It is required that subjects receiving oral corticosteroids begin a tapering regimen by Week 4. 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. • Budesonide should be reduced at a rate of 3 mg every 3 weeks until discontinuation.
Amended or new wording:	The maximum dose of oral corticosteroids for the treatment of CD that may be coadministered with vedolizumab IV is ~~30~~**20** mg/day prednisone or 9 mg/day budesonide (or equivalent) as long as the corticosteroid dose has been stable for at least 4 weeks prior to randomization. It is required that subjects receiving oral corticosteroids begin a tapering regimen by Week 4. ~~The~~**An example** 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. • Budesonide should be reduced at a rate of 3 mg every 3 weeks until discontinuation. **For patients who could not tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may have been increased up to the original dose at the start of study (should not exceed baseline dose). In such cases, the tapering regimen must be reinitiated within 2 weeks.**

Rationale for Change:

To reduce maximum dose of concomitant corticosteroid, to allow sites to follow their standard tapering schedule, and to clarify that that steroids can be increased back to the baseline dose if needed.

Change 19: Modified the criteria for discontinuation or withdrawal to add monitoring for leukopenia and lymphopenia and to clarify other criteria.

The primary change occurs in Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject:

Initial wording:

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

   - Liver Function Test (LFT) Abnormalities.

     Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.20), 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%).

…

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 (eg, withdrawal due to an AE or lack of efficacy).

Amended or new wording:

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

   - Liver Function Test (LFT) Abnormalities.

     Study ~~medication~~**drug** 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 9.1.20), if the following circumstances occur at any time during study ~~medication~~**drug** 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-MP, or methotrexate, if applicable, should be discontinued and the dose of vedolizumab held for an absolute lymphocyte count <0.5×10^9/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 ≥0.5×10^9/L. If the absolute lymphocyte count remains <0.5×10^9/L, study drug should be discontinued and the subject withdrawn from the study.**

…

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 **in the subject's source documents**.
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**~~eg~~, withdrawal due to an AE **should not be recorded in the voluntary *withdrawal category*. Similarly,** ~~or~~ lack of efficacy **should not be recorded in the *voluntary withdrawal* category**).

Rationale for Change:

To add monitoring for leukopenia and lymphopenia and to add clarifications to criteria 3 and 4.

Change 20: Clarified the medical history collection of smoking/nicotine usage status and collection of all medications for Crohn's disease.

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

Initial wording:	Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (as applicable), race as described by the subject, and smoking status of the subject at Screening. Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8.) … In addition, all prior biologic medication history for the treatment of CD, including date of diagnosis, with the reason for discontinuation is to be collected for subjects where possible.
Amended or new wording:	Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (as applicable), race as described by the subject, and smoking/**nicotine usage** 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~~**resolved** at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8.) … In addition, all prior biologic **and/or any** medication history for the treatment of CD, including date of diagnosis, with the reason for discontinuation is to be collected for subjects where possible.

Rationale for Change:

To capture relevant medical history information

Change 21: Clarified vital signs collection.

The primary change occurs in Section 9.1.6 Vital Sign Procedure:

Initial wording:	Vital signs will include body temperature (oral measurement), respiratory rate, supine blood pressure (resting more than 5 minutes), and pulse (resting more than 5 minutes).
Amended or new wording:	Vital signs will include body temperature ~~(oral measurement)~~, respiratory rate, supine blood pressure (**systolic and diastolic,** resting more than 5 minutes), and pulse (resting more than 5 minutes).

Rationale for Change:

To allow for sites that use tympanic body temperature and to clarify that blood pressure collection includes both systolic and diastolic.

Change 22: Clarified that all fistula draining assessments are preferably be done by the same qualified designee.

The primary change occurs in Section 9.1.11 Fistula Draining Assessment:

Added text: **Fistula draining assessment will preferably be performed by the same qualified designee for all assessments.**

Rationale for Change:

For consistency in endpoint measurement.

Appendix A Schedule of Study Procedures, footnote b, also contains this change.

Change 23: Clarified that confirmation from a central reader is required for magnetic resonance imaging eligibility.

The primary change occurs in Section 9.1.10 MRI Procedure:

Added text: **Confirmation must be obtained from a central reader to confirm MRI eligibility.**

Rationale for Change:

To clarify MRI eligibility requirements.

Change 24: Added the *superficial* category for the Parks classification.

The primary change occurs in Section 9.1.10.1 Parks Classification:

Added text: Parks described a classification system for perianal fistula [31], that will be used at Screening for classification of active fistula(e) as **superficial,** intersphincteric, transsphincteric, suprasphincteric, or extrasphincteric.

Rationale for Change:

To provide all categories for Parks classification.

Change 25: Clarified the neutralizing anti-vedolizumab antibodies (AVA) analysis.

The primary change occurs in Section 9.1.23 Anti-Vedolizumab Antibodies Sampling:

Added text: **A sample will be assessed for neutralizing AVA if a positive AVA is detected.**

Rationale for Change:

To clarify when neutralizing AVA will be analyzed.

Change 26: Replaced the existing Contraception and Pregnancy Avoidance language with 4 new subsections containing updated language for contraception and pregnancy avoidance, and clarified in Appendix C that highly effective contraception must be used.

The primary change occurs in Section 9.1.25 Contraception and Pregnancy Avoidance Procedure:

Deleted text:

~~For male subjects:~~

~~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.~~

~~For female subjects of childbearing potential:~~

~~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 post-vasectomy and have confirmed that~~

~~they have obtained documentation of the absence of sperm in the ejaculate.~~

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

~~**Barrier methods (each time the subject has intercourse):**~~	~~**Intrauterine devices (IUDs):**~~	~~**Hormonal contraceptives:**~~
~~• Male condom PLUS spermicide.~~	~~• Copper T PLUS condom or spermicide.~~	~~• Implants.~~
~~• Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.~~	~~• #Progesterone T PLUS condom or spermicide.~~	~~• Hormone shot/injection.~~
~~• Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.~~		~~• Combined pill.~~
		~~• Minipill.~~
		~~• Patch.~~
		~~• Vaginal ring PLUS male condom and spermicide.~~

~~Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.~~

~~During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving each IV dosing. At final study visit or early termination, subjects will have an additional serum pregnancy test.~~

Added text: ***9.1.25.1 Male Subjects and Their Female Partners***

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

9.1.25.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner must use a highly effective method of contraception (from the list below).**

In addition, they must be advised not to donate ova during this period.

9.1.25.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

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

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

The following procedures apply for contraception and pregnancy avoidance.

6. **Highly effective methods of contraception are defined as "those that, alone or in combination, result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:**
    - **Non-hormonal methods:**
        - **Intrauterine device (IUD).**
        - **Bilateral tubal occlusion.**
        - **Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.**
    - **Hormonal methods:**
        - **Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;**

- Oral.
- Intravaginal (eg, ring).
- Transdermal.

- Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
  - Oral.
  - Injectable.
  - Implantable.

7. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
8. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
9. During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a. Contraceptive requirements of the study
   b. Reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c. Assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)?

iv. Is there a chance you could be pregnant?

10. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses) and a negative urine hCG pregnancy test prior to receiving each IV dosing.

9.1.25.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- **Contraceptive requirements of the study.**
- **Reasons for use of barrier methods (ie, condom) in males with pregnant partners.**
- **Assessment of subject compliance through questions such as:**
  - **Have you used the contraception consistently and correctly since the last visit?**
  - **Have you forgotten to use contraception since the last visit?**
  - **Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?**
  - **Is there a chance you could be pregnant?**

Rationale for Change:

To add updated language for contraception and pregnancy avoidance to clarify acceptable/unacceptable forms of contraception and appropriate guidance for patients with regard to pregnancy avoidance during course of study and to clarify that highly effective contraception must be used in Appendix C.

Appendix C Elements of the Subject Informed Consent also contains this change.

Change 27: Clarified the pregnancy form requirement for female partners of male subjects.

The primary change occurs in Section 9.1.26 Pregnancy:

Added text: All pregnancies in subjects**, including female partners of male subjects,** on active study drug including comparator will be followed up to final outcome, using the pregnancy form.

Rationale for Change:

To clarify that pregnancy is followed for female partners of male subjects

Change 28: Added a requirement to document missed doses of antibiotic companion medication.

The primary change occurs in Section 9.2 Monitoring Subject Treatment Compliance:

Added text: **The site will also document missed doses of antibiotic companion medication.**

Rationale for Change:

To clarify that missed doses of companion medication should be documented.

Change 29: Changed wording in the safety section from *severity* to *intensity*.

The primary change occurs in Section 10.1.3 Additional Points to Consider for PTEs and AEs:

Initial wording:	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 is recorded.
Amended or new wording:	Changes in ~~severity~~**intensity** of AEs/Serious PTEs: • If the subject experiences changes in ~~severity~~**intensity** of an AE/serious PTE, the event should be captured once with the maximum ~~severity~~**intensity** is recorded.

Rationale for Change:

Update to preferred safety language

The following sections also contain this change:

- Section 10.1.6 Intensity of PTEs and AEs.
- Section 10.2.1.2 PTE and AE Reporting.
- Section 13.1.6 Safety Analysis.

Change 30: Added frequency to list of pretreatment event and adverse event reporting.

The primary change occurs in Section 10.2.1.2 PTE and AE Reporting:

Added text: **3. Frequency**

Rationale for Change:

Added per preferred safety language.

Change 31: Clarified that AVA titers are analyzed.

The primary change occurs in Section 13.1.5 Anti-vedolizumab Antibodies Analysis:

Added text: The proportion of subjects with positive **and titers of** AVA (transient and persistent), and proportion of subjects with positive neutralizing AVA during the study will be summarized.

Rationale for Change:

To clarify that titers of AVA are included in analysis.

Change 32: Clarified that the subject diary for Crohn's Disease Activity Index is electronic.

The primary change occurs in Appendix A Schedule of Study Procedures, footnote n:

Added text: (n) Subject **electronic** diary to be completed as per training instruction during screening interval. Subject **electronic** diary (CDAI and perianal pain) to be completed daily from Screening to Week 30.

Rationale for Change:

To clarify that footnote (n) in Appendix A refers to electronic diary.

Section 9.1.15 CDAI Diary Completion also contains this change.

Change 33: Clarified when serum versus urine pregnancy testing done.

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

Description of change:

- Row for "Pregnancy Testing" split into two rows to depict serum versus urine pregnancy testing.
- Serum pregnancy testing note at Screening and Final Visit/Early Termination.
- Urine pregnancy testing noted at Day 1, Weeks 2, 6, 10, 14, 22 and 40.

Rationale for Change:

To clarify when serum or urine testing is required in the table instead of in the footnotes.

Change 34: Clarified that pregnancy testing is performed before study drug dosing at dosing visits.

The primary change occurs in Appendix A Schedule of Study Procedures, footnote m:

Initial wording:	(m) Women of childbearing potential only. Urine pregnancy testing will be conducted at the site and serum pregnancy testing will be conducted by the central laboratory. Serum pregnancy completed at Screening and Week 30/Early Termination; urine pregnancy to be completed at other visits.
Amended or new wording:	(m) Women of childbearing potential only. Urine pregnancy testing will be conducted at the site and serum pregnancy testing will be conducted by the central laboratory. ~~Serum pregnancy completed at Screening and Week 30/Early Termination; urine pregnancy to be completed at other visits.~~**At visits with study drug dosing, to be performed before any study drug dosing.**

Rationale for Change:

To clarify in footnote (m) that pregnancy testing must be performed before study drug dosing.

Change 35: Added an investigator responsibility per updated International Conference on Harmonisation guideline.

The primary change occurs in Appendix B Responsibilities of the Investigator:

Added text: **13. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.**

Rationale for Change:

Added anew investigator responsibility per update in ICH guideline

Amendment 05 to A Randomized Double-Blind Phase 4 Study to Evaluate the Safety and Proportion of Subjects With Fistula Healing in 2 Dose Regimens of Entyvio (Vedolizumab IV) in the Treatment of Fistulizing Crohn's Disease (ENTERPRISE)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Pharmacovigilance Approval	26-Apr-2017 17:40 UTC
	Biostatistics Approval	27-Apr-2017 00:42 UTC
	Quality Control Approval	27-Apr-2017 10:14 UTC
	Medical Affairs Approval	27-Apr-2017 17:17 UTC