Title: An Open-Label, Phase 4 Study to Evaluate the Efficacy and Safety of Triple Combination Therapy With Vedolizumab IV, Adalimumab SC, and Oral Methotrexate in Early Treatment of Subjects With Crohn's Disease Stratified at Higher Risk for Developing Complications

NCT Number: NCT02764762

Protocol Approve Date: 30 June 2020

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

An Open-Label, Phase 4 Study to Evaluate the Efficacy and Safety of Triple Combination Therapy With Vedolizumab IV, Adalimumab SC, and Oral Methotrexate in Early Treatment of Subjects With Crohn's Disease Stratified at Higher Risk for Developing Complications

Triple Combination Therapy in High Risk Crohn's Disease

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421
Study Number:	Vedolizumab-4006
IND Number:	009125 EudraCT Number: Not applicable
Compounds:	Vedolizumab IV, Adalimumab SC, Methotrexate PO
Date:	30 June 2020 **Amendment Number:** 04

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
01 March 2016	Initial Protocol	Not applicable	Global
31 January 2017	01	Substantial	Global
12 March 2018	02	Substantial	Global
08 October 2018	03	Substantial	Global
30 June 2020	04	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
Serious adverse event and pregnancy reporting	Takeda Development Center Americas, Inc. Pharmacovigilance Department PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

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

PPD

1.3 Protocol Amendment 04 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment No. 04.

The primary purpose of this amendment is to update the protocol regarding addition of Monitr CD testing at Baseline Week 0, Week 26 and 102 or early termination. Monitr CD is a laboratory-developed test from Prometheus Labs that evaluates multiple markers of mucosal damage and repair processes, regardless of disease location. Other minor changes in procedures or definitions are proposed. Minor grammatical, editorial, formatting, and administrative changes are included for clarification and administrative purposes only. For specific descriptions of text changes and where the changes are located, see Appendix L.

The following is a summary of the changes made in Amendment No. 04:

1. Takeda address was updated.
2. Section 1.1 Robarts Medical Monitor phone was updated.
3. Section 1.1 Responsible Medical Officer contact was updated.
4. Sections 2.0 and 6.1 were updated to increase site number from 60-64.
5. Section 4.1.2.2 was updated with the latest exposure data from Investigator Brochure Edition 23 dated 12 July 2019.
6. Section 5.1.3 was updated to include the additional objective for Monitr CD testing.
7. Section 5.2.3 was updated to include endpoints for Monitr CD testing.
8. Sections 7.3.1.2, 8.1.3, 9.3.6, and Appendix A footnote (s) were updated to clarify exacerbation of CD language.
9. Section 7.4 Adverse Event withdrawal criteria was clarified to include criteria for Leukopenia or Lymphopenia.
10. Section 9.1.4 genitourinary system was removed from physical exam procedures.
11. Section 9.1.10 and Appendix A Schedule of Procedures table updated to include Monitr CD testing.
12. Section 9.1.11 and Appendix A Schedule of Procedures table and footnote (b) clarified colonoscopy may be performed at Early Termination visit.
13. Section 9.1.20 approximate total blood volume was updated.
14. Table 9.a was updated to include Monitr CD biomarkers.
15. Section 9.1.24 clarification of predose ADA sample collection timing.
16. Section 9.1.27.3 correction of reason for use of barrier methods (b).
17. Appendix A Schedule of Procedures table and footnote (j) were updated to clarify pregnancy testing for Q4 dosing.

18. Appendix A Schedule of Procedures footnote (a) was updated to clarify weight measurement visits.

INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compounds:** Vedolizumab intravenous (IV), Adalimumab subcutaneous (SC), Methotrexate oral (PO)	
Title of Protocol: An Open-Label, Phase 4 Study to Evaluate the Efficacy and Safety of Triple Combination Therapy With Vedolizumab IV, Adalimumab SC, and Oral Methotrexate in Early Treatment of Subjects With Crohn's Disease Stratified at Higher Risk for Developing Complications	**IND No.:** 009125	**EudraCT No.:** Not applicable
Study Number: Vedolizumab-4006	**Phase:** 4	

Study Design:

A phase 4, open-label, multicenter study in subjects with newly-diagnosed Crohn's disease (CD) at higher risk for complications due to aggressive disease. The study will investigate the efficacy and safety of triple combination therapy (300 mg vedolizumab IV, 160/80/40 mg adalimumab SC, and 15 mg oral methotrexate) over a 26-week treatment period for induction of endoscopic remission and mucosal healing followed by efficacy and safety of vedolizumab IV monotherapy to maintain remission for 76 weeks, for a total treatment period of 102 weeks.

The study will be conducted in the United States and Canada and will include 60 subjects with moderate to severe CD and judged by the investigator to be at moderate-high risk for complications. CD must have been diagnosed within the previous 24 months and subjects must be naïve to biologics.

Subjects who meet the inclusion criteria and none of the exclusion criteria will receive vedolizumab 300 mg IV infusion on Day 1 and Weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, and 102; adalimumab 160 mg SC injection on Day 2, 80 mg at Week 2, then 40 mg every 2 weeks thereafter until Week 26; and oral methotrexate 15 mg weekly from Day 1 through Week 34.

Primary Objectives:

- To determine the effect of triple combination therapy with an anti-integrin (vedolizumab IV), a tumor necrosis factor (TNF) antagonist (adalimumab SC), and an immunomodulator (oral methotrexate) on endoscopic remission at Week 26.

Secondary Objectives:

- To evaluate the effect of vedolizumab IV monotherapy on maintaining endoscopic remission at Week 102 following triple combination therapy.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on endoscopic healing at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on endoscopic response at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on deep remission at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on clinical remission by Crohn's Disease Activity Index (CDAI) at Weeks 10, 26, 52, 78, and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on clinical response by CDAI at Weeks 10, 26, 52, 78, and 102.

Additional Objectives:

- To evaluate the pharmacokinetics of vedolizumab and adalimumab in CD subjects at higher risk for CD complications at Week 26.
- To assess immunogenicity to vedolizumab and adalimumab over the follow-up period.

- To evaluate C-reactive protein (CRP) levels at Weeks 10 and 26.
- To evaluate fecal calprotectin at Weeks 10, 14, 26, 52, 78, and 102.
- To evaluate the impact of triple combination therapy on health-related quality-of-life (HRQOL) using the Inflammatory Bowel Disease Questionnaire (IBDQ), Work Productivity and Activity Impairment - Crohn's Disease (WPAI-CD), and the Inflammatory Bowel Disease Disability Index (IBD-DI).
- To evaluate endoscopic remission, defined as Monitr CD Endoscopic Healing Index (EHI) score ≤20, at Weeks 26 and 102.
- To evaluate Monitr CD EHI score ≤30 or ≤50 at Weeks 26 and 102.

Safety Objective:

- To evaluate the safety of triple combination therapy with an anti-integrin, a TNF antagonist, and an immunomodulator over a 26-week period, followed by 76 weeks of monotherapy with an anti-integrin.

Subject Population: Adult subjects at higher risk for progressive CD, with CD diagnosed within the previous 24 months. Subjects will be naïve to biologics.

Number of Subjects:	**Number of Sites:**
Approximately 60 subjects	Approximately 64 sites in the United States and Canada
Dose Level(s): Vedolizumab 300 mg IV at Weeks 0, 2, 6, and then every 8 weeks for total of 102 weeks. Adalimumab SC 160 mg at Week 0, 80 mg at Week 2, and then 40 mg every 2 weeks for a total of 26 weeks. Methotrexate 15 mg PO weekly for 34 weeks.	**Route of Administration:** Vedolizumab IV Adalimumab SC Methotrexate PO
Duration of Treatment: 102-week treatment period. Subjects will receive triple combination treatment for 26 weeks, followed by a 76-week treatment period of vedolizumab IV maintenance treatment for those who achieve clinical response (≥100-point decrease in CDAI).	**Period of Evaluation:** The study includes a 4-week screening period, a 26-week triple combination treatment period, an additional 76-week vedolizumab monotherapy treatment period (with last dose at Week 102), and a 26-week follow-up period following last dose. The duration of the study from screening to final study assessments at Week 120 will be approximately 124 weeks. All subjects will participate in a safety follow-up telephone call 26 weeks after last dose, for a total follow-up of 128 weeks.

Main Criteria for Inclusion:

- Adult subjects, aged 18 to 65 years at time of screening.
- CD diagnosed in the previous 24 months prior to screening.
- Simple Endoscopic Score for Crohn's Disease (SES-CD) score ≥7 (or ≥4 if isolated ileal disease).
- Subjects judged by the investigator as having CD at moderate-high risk for complications based on clinical assessment, the Crohn's Disease Personalized Risk and Outcome Prediction Tool (PROSPECT), or criteria defined by the 2014 American Gastroenterology Association (AGA) CD care pathway.
- If a subject is on corticosteroids, they must be willing to follow a mandatory taper of prednisone or budesonide within 60 days after enrollment.
- If a subject is on 5-aminosalicylate (5-ASA), antibiotics, or probiotic, they must be willing to stop that treatment at enrollment.

Main Criteria for Exclusion:

- Subjects who have any evidence of active infection during Screening.
- Subjects who have a history of any bacterial, viral, and other infection due to opportunistic pathogens.
- History of tuberculosis (TB), a chest radiograph suggestive of TB infection, or positive tuberculin skin test with purified protein derivative OR positive QuantiFERON GOLD test.
- Subjects who have had prior exposure to any TNF antagonist biologic therapy, or to vedolizumab, natalizumab, efalizumab, or rituximab.
- Any prior CD-related surgery or CD complication requiring surgery.
- History of any lymphoma or lymphoproliferative disease.
- History of congestive heart failure (New York Heart Association class III/IV) or unstable angina.
- Subjects with a medical history that contraindicates the use of methotrexate or adalimumab or indicates an intolerance to methotrexate or adalimumab.

Main Criteria for Evaluation and Analyses:

Primary endpoint: Percentage of subjects achieving endoscopic remission (defined as SES-CD 0-2) at Week 26.

Secondary endpoints:

- Percentage of subjects achieving endoscopic healing defined as SES-CD ≤4 AND reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Week 26.
- Percentage of subjects achieving endoscopic response defined as 50% reduction in SES-CD from baseline at Week 26.
- Change from baseline SES-CD score at Week 26.
- Percentage of subjects achieving deep remission (defined as CDAI<150 and SES-CD 0-2) at Week 26.
- Percentage of subjects achieving clinical remission (defined as CDAI <150) AND endoscopic response as a measure of mucosal healing (defined as 50% reduction in SES-CD from baseline) at Week 26.
- Percentage of subjects achieving clinical remission (CDAI score <150) at Weeks 10 and 26.
- Percentage of subjects achieving clinical response (defined as ≥100-point decrease in CDAI score) at Weeks 10 and 26.
- Change from baseline CRP levels at Weeks 10 and 26.
- Change in fecal calprotectin concentrations from baseline at Weeks 10, 14, 26, 52, 78, and 102.
- Percentage of subjects achieving clinical remission (defined as CDAI <150) AND CRP <5 (in subjects with elevated CRP at baseline) at Weeks 26, 52, 78, and 102.
- Percentage of subjects using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission (CDAI score <150) at Weeks 10, 26, and 102.
- Percentage of subjects maintaining clinical remission (defined as CDAI <150) at Weeks 52, 78, and 102.
- Percentage of subjects maintaining endoscopic remission defined as SES-CD 0-2 at Week 102.
- Percentage of subjects maintaining deep remission (defined as CDAI <150 and SES-CD 0-2) at Week 102.
- Percentage of subjects maintaining endoscopic healing defined as SES-CD ≤4 AND reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Week 102.
- Percentage of subjects maintaining endoscopic response defined as 50% reduction in SES-CD from baseline at Week 102.
- Percentage of subjects maintaining clinical remission (defined as CDAI <150) AND endoscopic response as a measure of mucosal healing (defined as 50% reduction in SES-CD from baseline) at Week 102.
- Percentage of subjects with first exacerbation of CD after 26 weeks (defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, objective evidence of disease activity by colonoscopy,

AND CRP above normal, OR fecal calprotectin >250 µg/g alone).

Additional endpoints:

- Change from baseline IBDQ score at Weeks 14, 26, 52, 78, and 102.
- Change from baseline WPAI-CD score at Weeks 14, 26, 52, 78, and 102.
- Change from baseline in IBD-DI score at Weeks 14, 26, 52, 78, and 102.
- Percentage of subjects achieving normalization of CRP defined as <5 mg/L at Week 26 (in those elevated at baseline).
- Trough concentration of vedolizumab and adalimumab at Week 26.
- Change from baseline of Patient Reported Outcome 2 (PRO-2) score at Weeks 26, 52, 78, and 102.
- Change from Week 26 CDAI score at Weeks 52, 78, and 102.
- Change from Week 26 PRO-2 score at Weeks 52, 78, and 102.
- Change from Week 26 CRP levels at Weeks 52, 78, and 102.
- Percentage of subjects with positive antidrug antibodies (ADAs) to vedolizumab and adalimumab, and neutralizing ADAs (nADAs) to vedolizumab. (Percentage of subjects with nADAs to adalimumab is optional if deemed necessary for the interpretation of the data).
- Time to major CD-related events (hospitalizations, bowel surgeries, procedures).
- Percentage of subjects hospitalized from Day 1 to Week 102.
- Percentage of subjects requiring surgery other than seton placement for perianal fistula from Day 1 to Week 102.
- Percentage of subjects achieving a PRO-2 score ≤75 and an SES-CD ≤4 AND a reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Weeks 26 and 102.
- Percentage of subjects assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.
- Percentage of subjects developing a CD-related complication by Week 102 who were assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.
- Percentage of subjects with an EHI score ≤20 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤30 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤50 at Weeks 26 and 102.
- Change from baseline in EHI at Weeks 26 and 102.

Safety Endpoints:

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

Statistical Considerations:

For all dichotomous endpoints, corresponding rates and a 95% CIs will be reported.

Time-to-event endpoints will be analyzed by survival analysis procedures estimated by Kaplan-Meier product limit methods and presented with appropriate 95% CIs.

Change from baseline in CDAI and PRO-2 scores will be analyzed using Wilcoxon signed-rank test for paired data; the median change and its nonparametric 95% CI will also be presented.

Other endpoints will be summarized descriptively.

Sample Size Justification:

The sample size was based on an estimate of precision. A sample size of 60 subjects will generate a 95% CI for endoscopic remission (defined as SES-CD 0-2) at Week 26 with a half width no wider than 12.7% and expected remission of 50%. If the expected remission rate is different from 50%, a required sample size would be smaller.

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 medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-ASA	5-aminosalicylate
Act-1	murine predecessor to vedolizumab antibody
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
AGA	American Gastroenterology Association
ALT	alanine aminotransferase
ASCA	anti-*Saccharomyces cerevisiae* antibody
AST	aspartate aminotransferase
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CIMS	Central Image Management Solution
CRO	contract research organization
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
EHI	endoscopic healing index
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
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
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBD-DI	Inflammatory Bowel Disease Disability Index
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG1	immunoglobulin G1

INR	international normalized ratio
IP	Investigational Product
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
IRT	interactive response technology
JCV	John Cunningham virus
LFT	liver function tests
LTFU	long-term follow-up
LTS	long-term safety
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
Med ID	medication identification number
Monitr CD	Monitr Crohn's Disease
nADA	neutralizing antidrug antibodies
NOD2	nucleotide-binding oligomerization domain-containing protein 2
NSAID	nonsteroidal anti-inflammatory drug
pANCA	perinuclear antineutrophil antibody
PC	product complaint
PD	pharmacodynamic(s)
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PO	orally
PP	per protocol
PRO-2	Patient Reported Outcome 2
PROSPECT	Crohn's Disease Personalized Risk and Outcome Prediction Tool
PTE	pretreatment event
Q4W	every 4 weeks
Q8W	every 8 weeks
RAMP	Risk Assessment and Minimization for PML
RCF	relative centrifugal force
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TNF	tumor necrosis factor

TNF-α	tumor necrosis factor-alpha
TNF-β	tumor necrosis factor-beta
TYSABRI	natalizumab
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VCAM-1	vascular cell adhesion molecule-1
WBC	white blood cell
WHODRUG	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential
WPAI-CD	Work Productivity and Activity Impairment - Crohn's Disease

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Americas
Takeda	TDC Americas

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 [1]. 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.

Untreated CD patients commonly develop structural complications that include stricture and fistula formation, which commonly result in hospitalizations and surgery over time. When examining 306 CD patients from the United States, Thia et al. showed that the cumulative risk of developing CD complications of either stricturing or penetrating disease was 33.7% at 5 years and 50.8% at 20 years after establishment of CD diagnosis [2]. The natural course of the disease can range from an indolent course with prolonged periods of remission to aggressive, incapacitating disease associated with structural bowel wall damage. Certain patients have aggressive CD, which could be defined as having a high relapse rate, development of penetrating disease, need for repeat surgery, or multiple admissions for flares [3]. The pathophysiology of IBD is complex as multiple environmental factors interact with the genotype of an individual to cause expression of disease. Published risk factors for aggressive disease include involvement of the upper GI tract and ileum, penetrating disease, early age at diagnosis, smoking, extensive ulceration of the mucosa, high titers of certain serum antibodies, and mutations of the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene [4]. The ability to more readily predict which patients will be at higher risk for complications and target more intensive, early treatment to that group would be invaluable. The 2014 American Gastroenterology Association (AGA) Clinical Care Pathway outlined criteria for patients considered at moderate-high risk for disease complications that included: <30 years of age at initial diagnosis, extensive anatomic involvement, perianal or severe rectal disease, deep ulcers, prior surgical resection or structuring, and/or penetrating behavior [5]. Additionally, the Crohn's Disease Personalized Risk and Outcome Prediction Tool (PROSPECT), which incorporates clinical, serological, and genetic variables, has been developed by Siegel et al. This tool is used to predict the probability of developing complications related to CD, specifically strictures or internal penetrating disease. The output of the predictive model allows risk stratification of patients from low to medium to high risk of complications within a 3-year period [4,6].

4.1.2 Vedolizumab

Vedolizumab (also called MLN0002) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [7-10]. Vedolizumab binds the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and as such, impairs the migration of gut homing lymphocytes into GI mucosa. As a result, vedolizumab acts as a gut-selective immunomodulator [11].

Vedolizumab IV (also known as ENTYVIO; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion; or MLN0002 IV) has been granted marketing approval in multiple countries globally. Vedolizumab intravenous (IV) is approved for the treatment of adult patients with moderately to severely acute UC or CD who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. 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

Nonclinical in vitro and in vivo studies have been conducted with vedolizumab and its murine homologue, murine predecessor to vedolizumab antibody (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 α4β1 integrin [11].

4.1.2.2 Human Experience

As of 19 May 2019, approximately 6376 subjects (679 healthy subjects, 2671 subjects with UC, and 2920 subjects with CD) have received at least 1 dose of vedolizumab across all studies in the clinical development program (see current version of Investigator's Brochure). Vedolizumab exposure has extended for ≥12 months in 2553 subjects, ≥24 months in 1636 subjects, ≥36 months in 1126 subjects, ≥48 months in 908 subjects, ≥60 months in 675 subjects, and ≥72 months in 378 subjects as of 19 May 2019. Based on drug shipment data, the patient exposure to vedolizumab since its approval in May 2014 is estimated to be approximately 336,400 patient-years.

In subjects with moderately to severely active CD (Study C13007), including subjects who had failed treatment with 1 or more therapies including tumor necrosis factor-alpha (TNF-α) antagonists, vedolizumab 300 mg infusion at Weeks 0 and 2 (induction) followed by either once every 4 weeks (Q4W) or Q8W from Weeks 6 through 52 (maintenance) demonstrated differences in efficacy compared to placebo for both the Induction Phase and Maintenance Phase. The study met its primary endpoint for the Induction Phase, clinical remission at Week 6, but did not meet the second primary endpoint of enhanced clinical response (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 [12].

Rates of mucosal healing were recently reported in 27 CD subjects who received IV vedolizumab monotherapy. Mucosal healing was reported in 30% of subjects who had a baseline colonoscopy before vedolizumab, 73% of whom were not TNF-antagonist naïve. The subjects' second colonoscopy occurred 12 to 52 weeks after vedolizumab induction (median of 22 weeks). Mucosal healing was defined as an absence of ulceration. Endoscopic improvement was 52% [13].

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 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 trials experience, see full prescribing information [14].

4.1.3 Adalimumab

Adalimumab is a recombinant human IgG1 mAb specific for human TNF-α. Adalimumab binds specifically to TNF-α and blocks its interaction with the p55 and p75 cell surface TNF-α receptors.

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

Adalimumab is approved globally for the treatment of moderately to severely active CD in patients who have had an inadequate response to conventional therapy. Additionally, adalimumab is approved for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Adalimumab 40 mg weekly or every other week has been shown to be effective for maintaining clinical remission in patients with CD who have responded to adalimumab induction therapy. Adalimumab has also been shown to have corticosteroid-sparing effects in patients with CD [15].

In CLASSIC I, a dose ranging, randomized, controlled induction trial of adalimumab, 299 subjects with moderate to severe CD who were naïve to TNF-α antagonists were evaluated. The study demonstrated that an adalimumab loading dose regimen of 160 mg subcutaneous (SC) at Week 0 and 80 mg SC at Week 2 was significantly more effective than placebo (36% vs 12%, p=0.001). CLASSIC II, a maintenance follow-up trial to CLASSIC I, demonstrated that adalimumab SC every other week or weekly was superior to placebo in maintaining remission over a 56-week period in 55 subjects with moderate to severe CD naïve to TNF-antagonist therapy who experienced remission with adalimumab induction therapy. In this rerandomized cohort of 55 subjects, 79% who received adalimumab 40 mg every other week and 83% who received 40 mg weekly maintained remission through Week 56 (primary endpoint) compared with 44% for placebo ($p< 0.05$ for both adalimumab groups vs placebo). The subjects from CLASSIC I who had not been in remission entered an open-label arm and received adalimumab 40 mg every other week (dosages could be increased to 40 mg weekly if there was a nonresponse or flare) [16].

The CHARM study included 854 subjects with moderate to severe CD who were TNF antagonist therapy naïve, had been exposed to infliximab in the past, and had either lost response or become intolerant to infliximab. The primary endpoint was clinical remission at Weeks 26 and 56 among subjects who responded to adalimumab. The subjects received open-label adalimumab SC at doses of 80 mg at Week 0 and 40 mg at Week 2 with response defined by a decrease in CDAI score of 70 points at Week 4. Overall, 499 (approximately 60%) subjects responded at Week 4 and were randomized to 1 of 3 treatment arms: adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo. At Week 26, 40% of the adalimumab 40-mg every other week group, 47% of the adalimumab 40 mg weekly group, and 17% of the placebo group were in remission (p=0.001 for both groups compared to placebo, no difference between active groups). This benefit was maintained out to Week 56 with 36% of the adalimumab 40 mg every-other-week group, 41% of the adalimumab 40 mg weekly group, and 12% of the placebo group remaining in remission (p=0.001) [17].

The GAIN study, a placebo-controlled, randomized, controlled trial evaluated 325 subjects with moderate to severe CD who had failed infliximab therapy (defined as intolerant of infliximab or having previously responded then lost response to infliximab). Subjects were treated with adalimumab (160 mg at Week 0 then 80 mg at Week 2) or placebo. A total of 301 subjects completed the trial, and at Week 4 induction of remission was greater for adalimumab than for placebo (21% vs 7% p<0.001) [18].

Adalimumab was well tolerated in the efficacy-based studies discussed above. SAEs have been reported in 25% of patients, including injection-site reactions (20%), malignant neoplasm (1.7%), opportunistic infection (2.1%), and tuberculosis ([TB] 0.2%). Other adverse events (AEs) associated with adalimumab include increased risk of infections, antibody formation, autoimmunity, skin eruption, abnormal liver function tests (LFTs), demyelization, and congestive heart failure.

4.1.4 Methotrexate

Methotrexate is an antimetabolite that is approved for the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Methotrexate was originally developed as an antineoplastic, and is an inhibitor of the enzyme dihydrofolate reductase, which catalyzes a reaction in the production of tetrahydrofolic acid. This pathway is essential to the synthesis of the purine and pyrimidine components of DNA, and thus the drug slows cellular division. Although the mechanism of action of low-dose methotrexate in the treatment of autoimmune disease is not well understood, there is evidence supporting both immunosuppressive and anti-inflammatory effects.

In rheumatoid arthritis, methotrexate is a mainstay of treatment because of its excellent anti-inflammatory effect, rapid onset of action, and acceptable safety profile. Recently, methotrexate has become the agent of choice for combination therapy with the newer biologics in rheumatoid arthritis [19], [20], [21], [22].

TNF antagonist therapy and methotrexate appear to have additive effects with respect to efficacy in rheumatoid arthritis. In CD, the additive effect may be relevant from a mechanistic perspective since both drugs induce apoptosis. Cell death mechanisms and apoptosis are important to the pathogenesis of CD.

Following oral administration of low-dose methotrexate (<5 mg), absorption approaches 100%. The peak blood concentration is observed within 1 to 2 hours. Methotrexate is 50% protein bound, displacement occurs in competition with other highly protein-bound compounds, and distribution is widespread. In 1987, Kozarek was the first to report the results of intramuscular methotrexate therapy in patients with refractory IBD (14 CD; 7 UC) and two-thirds of patients with steroid refractory disease showed an improvement in symptoms and a concomitant reduction in prednisone requirements [23]. Some patients demonstrated endoscopic remission. In subsequent studies when methotrexate was used as a monotherapy in patients requiring corticosteroids, response rates were suboptimal [24]. The use of methotrexate for induction and maintenance therapy in CD was definitively established based on the results of the placebo-controlled trials of the North American Crohn's Study Group Investigators published in 1995 and 2000 [25], [26]. In

these studies, steroid-dependent CD patients treated with 25 mg methotrexate intramuscularly each week achieved steroid-free remission rates in 39% compared with 19% on placebo, and maintained remission with 15 mg methotrexate per week in 65% compared with 39% on placebo. In spite of these excellent clinical data for methotrexate in CD, it has never been widely utilized as a monotherapy in adults but is increasingly used clinically in combination with biologic therapy to reduce immunogenicity [24]. The combination of maintenance methotrexate and infliximab in the COMMIT trial is the most recent study to demonstrate immunogenicity efficacy of methotrexate on infliximab trough and anti-infliximab antibody levels [27]. The study did not, however, reveal a difference in clinical outcomes between combination methotrexate/infliximab and infliximab monotherapy, despite the positive effects of methotrexate on antibody formation to infliximab and infliximab trough levels. These results are in contrast to the results of the study of biologic and immunomodulatory-naive patients in the SONIC CD study, which demonstrated an increased effectiveness of azathioprine/infliximab combination therapy compared with infliximab monotherapy in inducing and maintaining remission, and was corroborated by higher infliximab trough levels and lower anti-infliximab antibodies [28].

The most frequently observed adverse event of methotrexate therapy is nausea (in up to 25% of treated patients), which often can be well-controlled and/or avoided with concomitant ondansetron tablets given 1 to 2 hours before and 12 to 24 hours after methotrexate administration [24]. Methotrexate also may cause bone marrow suppression. In 1 series, mild leukopenia (white blood cell [WBC] count 2.8-4.0×10^9/L) was encountered at least once in 21% of patients with rheumatoid arthritis treated with 15 mg weekly [29]. In all cases, leukopenia was transient, responded to minimal dose reduction, and did not lead to cessation of therapy. Although severe leukopenia and associated infection has been reported with methotrexate, it is rare with low-dose therapy. Leukopenia is usually correctable by dose reduction and is almost always asymptomatic. Thrombocytopenia is rarely seen. Additionally, acute pulmonary toxicity is an uncommon adverse reaction to methotrexate. This hypersensitivity reaction presents with acute dyspnea associated with bilateral alveolar or interstitial pulmonary changes. A high clinical index of suspicion and prompt treatment with steroids usually leads to resolution without chronic sequelae. No increased incidence of cancer or lymphoma has been reported for methotrexate although overall rates of use are lower than that of other immunomodulator therapies [24]. Methotrexate may promote rise of liver enzymes, which is observed in 3% to 33% of IBD patients treated with methotrexate, and necessitates discontinuing therapy in around 6% to 8% [24]. Recommendations for stopping therapy are based on the degree of absolute change in liver enzymes and the duration of abnormalities on serial measurements. Underlying liver diseases such as nonalcoholic fatty liver disease, diabetes, or excess alcohol consumption are important cofactors for methotrexate-induced liver toxicity. However, methotrexate-associated advanced liver fibrosis is rarely seen in patients with IBD or rheumatoid arthritis. Other GI complaints including stomatitis and diarrhea are less common. The teratogenic effects of methotrexate are well established.

4.2 Rationale for the Proposed Study

CD is a chronic inflammatory disorder of the GI tract. Treatment with TNF-antagonist therapy substantially improved the care of patients with CD refractory to corticosteroids,

immunomodulators, and mesalamine. In 2010, the SONIC trial demonstrated that combination therapy with the TNF antagonist infliximab and immunomodulator azathioprine further significantly improved treatment efficacy [30]. About 40% of patients, however, will not achieve remission after initiation of a combined TNF antagonist and immunomodulator [30]. This raises the question as to whether we can improve remission rates and modify disease progression by adding a third agent, vedolizumab, with a different mechanism of action to TNF antagonists, to the combination regimen, particularly for patients who are at higher risk for CD complications.

Vedolizumab is an α4β7 anti-integrin, approved in the United States in 2014 to treat both moderate to severe CD and UC and in Canada in 2015 to treat UC, after demonstrating efficacy and safety in the GEMINI studies [12,31,32]. Subjects who have failed TNF-antagonist therapy have been shown to have higher levels of tissue MAdCAM and lower levels of circulating α4β7-positive cells. Subjects who responded to therapy with infliximab or adalimumab have been shown to have a decrease in MAdCAM and an increase in α4β7-positive cells [33]. This suggests that the vedolizumab pathway is active and that vedolizumab may work well as part of a combination therapy regimen. Combining biologic therapies with alternate mechanisms of action, such as the anti-integrin vedolizumab and the TNF antagonist adalimumab, may provide clinically relevant synergy.

There is growing evidence that mucosal healing is an important outcome in CD treatment. Rutgeerts et al. demonstrated this in the postoperative setting showing that CD patients with endoscopic evidence of active disease were more likely to have a clinical recurrence in the following 4 to 8 years [34]. In clinical trials with biologics, patients who have mucosal healing have been shown to have increased rates of steroid-free remission and a decreased risk of surgery and hospitalization [35]. In view of these findings, clinical practice is moving toward a "treat to target" approach, where the goals of treatment go beyond controlling symptoms and instead aim for improving objective measures such as mucosal healing and deep remission [36].

Further subgroup analyses in CD biologic clinical trials have demonstrated higher response rates in patients who are treated earlier in the course of their disease (less than 1 or 2 years from diagnosis). In a recent study, using a combination of a TNF antagonist, infliximab, and azathioprine, clinical remission and full mucosal healing was observed in more than 65% of patients with early disease of less than 18 months in duration [37,38]. The REACT trial demonstrated that early introduction of combination therapy with adalimumab and an immunomodulator decreased the chance of hospitalizations, complications, and surgeries at 2 years compared to conventional therapy [39].

Importantly, our understanding of which patients with CD are at higher risk for an aggressive disease course has improved, as various risk factors are identified and predictive tools have been developed [6,40]. Involvement of the upper GI tract and ileum, penetrating disease, early age at diagnosis, smoking, extensive ulceration of the mucosa, high titers of serum antibodies, and mutations of the NOD2 gene all have been determined to be markers of aggressive CD [3].This can allow for targeting of earlier combination therapy for those at highest risk.

The hypothesis of this study is that triple combination therapy with 2 biologics with different mechanisms of action (the anti-integrin vedolizumab IV and the TNF antagonist adalimumab SC)

and an immunomodulator (oral methotrexate) will be effective and have an acceptable safety profile at inducing endoscopic remission over a 26-week period. Endoscopic remission will be defined as a Simple Endoscopic Score for Crohn's Disease (SES-CD) 0 to 2. Only subjects with suspected aggressive CD at increased risk for disease complications will be enrolled in the study. By investigator judgement, subjects will be assessed as having CD at moderate-high risk for complications based on clinical assessment, the PROSPECT tool, or criteria defined by the 2014 AGA CD Clinical Care Pathway [4-6]. Importantly, the triple combination approach is hypothesized to modify disease progression in newly diagnosed CD subjects at higher risk for complications related to more aggressive disease.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to determine the effect of triple combination therapy with an anti-integrin (vedolizumab IV), a TNF antagonist (adalimumab SC), and an immunomodulator (oral methotrexate) on endoscopic remission at Week 26.

5.1.2 Secondary Objectives

- To evaluate the effect of vedolizumab IV monotherapy on endoscopic remission at Week 102 following triple combination therapy.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on endoscopic healing at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on endoscopic response at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on deep remission at Weeks 26 and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on clinical remission by CDAI at Weeks 10, 26, 52, 78, and 102.
- To evaluate the effect of triple combination therapy followed by vedolizumab monotherapy on clinical response by CDAI at Weeks 10, 26, 52, 78, and 102.

5.1.3 Additional Objectives

Additional objectives include:

- To evaluate the PK of vedolizumab and adalimumab in CD subjects at higher risk for complications at Week 26.
- To assess immunogenicity to vedolizumab and adalimumab over the follow-up period.

- To evaluate C-reactive protein (CRP) levels at Weeks 10 and 26.
- To evaluate fecal calprotectin at Weeks 10, 14, 26, 52, 78, and 102.
- To evaluate the impact of triple combination therapy on health-related quality-of-life (HRQOL) using the Inflammatory Bowel Disease Questionnaire (IBDQ), Work Productivity and Activity Impairment - Crohn's Disease (WPAI-CD), and the Inflammatory Bowel Disease Disability Index (IBD-DI).
- To evaluate endoscopic remission, defined as Monitr CD Endoscopic Healing Index (EHI) score ≤20, at Weeks 26 and 102.
- To evaluate Monitr CD EHI score ≤30 or ≤50 at Weeks 26 and 102.

5.1.4 Safety Objective

The safety objective is to evaluate the safety of triple combination therapy with an anti-integrin, a TNF antagonist, and an immunomodulator over a 26-week period, followed by 76 weeks of monotherapy with an anti-integrin.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint is the percentage of subjects achieving endoscopic remission (defined as an SES-CD 0-2) at Week 26.

5.2.2 Secondary Endpoints

Secondary endpoints are as follows:

- Percentage of subjects achieving endoscopic healing defined as SES-CD ≤4 AND reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Week 26.
- Percentage of subjects achieving endoscopic response defined as 50% reduction in SES-CD from baseline at Week 26.
- Change from baseline SES-CD score at Week 26.
- Percentage of subjects achieving deep remission (defined as CDAI<150 and SES-CD 0-2) at Week 26.
- Percentage of subjects achieving clinical remission (defined as CDAI <150) AND endoscopic response as a measure of mucosal healing (defined as 50% reduction in SES-CD from baseline) at Week 26.
- Percentage of subjects achieving clinical remission (CDAI score <150) at Weeks 10 and 26.
- Percentage of subjects achieving clinical response (defined as ≥100-point decrease in CDAI score) at Weeks 10 and 26.

- Change from baseline CRP levels at Weeks 10 and 26.
- Change in fecal calprotectin concentrations from baseline at Weeks 10, 14, 26, 52, 78, and 102.
- Percentage of subjects achieving clinical remission (defined as CDAI <150) AND CRP <5 (in subjects with elevated CRP at baseline) at Weeks 26, 52, 78, and 102.
- Percentage of subjects using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission (CDAI score <150) at Weeks 10, 26, and 102.
- Percentage of subjects maintaining clinical remission (defined as CDAI <150) at Weeks 52, 78, and 102.
- Percentage of subjects maintaining endoscopic remission defined as SES-CD 0-2 at Week 102.
- Percentage of subjects maintaining deep remission (defined as CDAI <150 and SES-CD 0-2) at Week 102.
- Percentage of subjects maintaining endoscopic healing defined as SES-CD ≤4 AND reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Week 102.
- Percentage of subjects maintaining endoscopic response defined as 50% reduction in SES-CD from baseline at Week 102.
- Percentage of subjects maintaining clinical remission (defined as CDAI <150) AND endoscopic response as a measure of mucosal healing (defined as 50% reduction in SES-CD from baseline) at Week 102.
- Percentage of subjects with first exacerbation of CD after 26 weeks (defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, objective evidence of disease activity by colonoscopy AND CRP above normal, OR fecal calprotectin >250 μg/g alone).

5.2.3 Additional Endpoints

Additional endpoints include the following:

- Change from baseline IBDQ score at Weeks 14, 26, 52, 78, and 102.
- Change from baseline WPAI-CD score at Weeks 14, 26, 52, 78, and 102.
- Change from baseline in IBD-DI score at Weeks 14, 26, 52, 78, and 102.
- Percentage of subjects achieving normalization of CRP defined as <5 mg/L at Week 26 (in those elevated at baseline).
- Trough concentration of vedolizumab and adalimumab at Week 26.
- Change from baseline of Patient Reported Outcome 2 (PRO-2) score at Weeks 26, 52, 78, and 102.

- Change from Week 26 CDAI score at Weeks 52, 78, and 102.
- Change from Week 26 PRO-2 score at Weeks 52, 78, and 102.
- Change from Week 26 CRP levels at Weeks 52, 78, and 102.
- Percentage of subjects with positive antidrug antibodies (ADAs) to vedolizumab and adalimumab, and neutralizing ADAs (nADAs) to vedolizumab. (Percentage of subjects with nADAs to adalimumab is optional if deemed necessary for the interpretation of the data).
- Time to major CD-related events (hospitalizations, bowel surgeries, and CD-related procedures).
- Percentage of subjects hospitalized from Day 1 to Week 102.
- Percentage of subjects requiring surgery other than seton placement for perianal fistula from Day 1 to Week 102.
- Percentage of subjects achieving a PRO-2 score ≤75 AND an SES-CD ≤4 AND a reduction from baseline SES-CD of at least 2 points AND no individual SES-CD subscore >1 at Weeks 26 and 102.
- Percentage of subjects assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.
- Percentage of subjects developing a CD related complication by Week 102 who were assessed at screening as having moderate-high risk CD with ≥20% chance of disease complication by Year 2 as calculated by the PROSPECT predictive tool for those for whom that tool was used.
- Percentage of subjects with an EHI score ≤20 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤30 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤50 at Weeks 26 and 102.
- Change from baseline in EHI score at Weeks 26 and 102.

5.2.4 Safety Endpoints

Safety will be assessed by AEs, adverse events of special interest (AESIs), SAEs, AEs leading to discontinuation, vital signs, physical examination, 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, open-label, multicenter study in subjects with newly-diagnosed CD at higher risk for complications due to aggressive disease. The study will investigate the efficacy and safety of triple combination therapy (300 mg vedolizumab IV, 160/80/40 mg adalimumab SC, and 15 mg

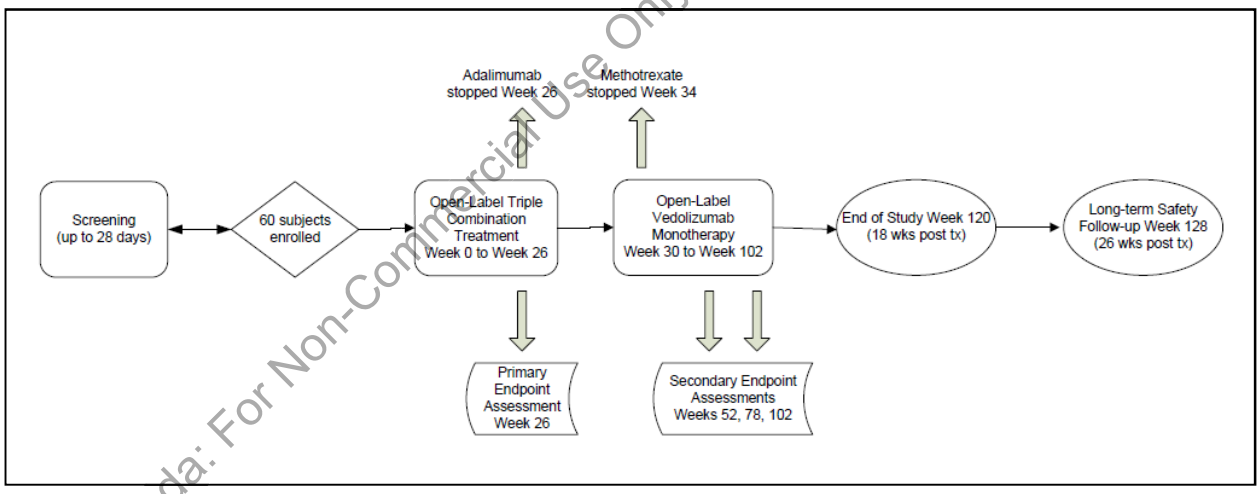
oral methotrexate) over a 26-week treatment period for induction of clinical endoscopic remission and mucosal healing followed by efficacy and safety of vedolizumab IV monotherapy to maintain remission for 76 weeks, for a total treatment period of 102 weeks.

Approximately 60 subjects with moderate to severe active CD at higher risk for disease complications will be studied at approximately 64 sites in the United States and Canada. Subjects must be diagnosed with CD within the previous 24 months and be naïve to biologics. Subjects will be determined to be at increased risk of CD complications. Subjects at low risk for CD complications will be excluded. Subjects will be followed for a total of 128 weeks.

The study consists of up to a 4-week screening period, a 26-week combination treatment period, an additional 76-week vedolizumab IV monotherapy treatment period, and a 26-week follow-up period following last dose (with final efficacy evaluations at Week 120). The duration of the study from screening to final efficacy visit at Week 120 will be approximately 124 weeks. All subjects, including subjects who discontinue early, will participate in a safety follow-up telephone call 26 weeks after last dose, for a total follow-up of 128 weeks.

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

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

The aim of the current study is to evaluate the efficacy and safety of triple combination therapy of vedolizumab, adalimumab, and methotrexate in the induction of clinical remission and endoscopic healing and remission as a measure of mucosal healing of subjects with newly diagnosed CD at higher risk for complications due to aggressive disease followed by efficacy and safety of vedolizumab monotherapy to maintain remission. Therapeutic goals for CD have evolved from control of symptoms to mucosal healing. Achieving clinical remission, biomarker remission, and mucosal healing has become one of the treatment goals for subjects with CD and is associated with

better outcomes of steroid-free remission and decreased risk of surgery and hospitalization. Complete mucosal healing, however, is only achieved by a minority of subjects in clinical practice and trials. The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the SES-CD are robust, validated, endoscopic indices that show high reproducibility among central readers [41]. The absence of validated score thresholds associated with specific prognostic values or with endoscopic healing, however, represents a weakness of both the CDEIS and the SES-CD. While most thresholds for remission in trials have been chosen arbitrarily by investigators, specialists in the field of IBD recently agreed on a SES-CD of 0–2 for the definition of endoscopic remission. Endoscopic response as a >50% decrease in SES-CD was also proposed [41].

There are different treatment agents and combinations used currently in clinical practice to achieve the goal of endoscopic and clinical remission. Combination therapy for CD appears to lead to significantly improved efficacy; however, many subjects treated with combined TNF-antagonist and immunomodulator therapy do not achieve mucosal healing [30]. Vedolizumab has a unique, gut-selective, immunomodulatory mechanism of action that provides the basis for its development as a treatment for CD. In a pivotal phase 3 clinical trial, vedolizumab IV was effective for induction and maintenance therapy in subjects with CD [12]. The goal of adding vedolizumab, which has a different mechanism of action, to a TNF antagonist and immunomodulator, is to safely and effectively improve remission rates in CD patients. Coadministration of the 2 biologics infliximab and natalizumab was previously studied for 10 weeks in 52 CD subjects and was well tolerated without increased adverse events compared to infliximab monotherapy [42].

The primary endpoint evaluated in this study will be endoscopic remission at Week 26. Based on a post hoc analysis of the SONIC trial, 26 weeks is the minimum time for the majority of patients to achieve deep remission with combination therapy [43]. CD patients treated early in their course of disease with combination therapy have reduced chances of hospitalization, complications, and surgeries [39].

Our understanding of which patients with CD are at higher risk for aggressive disease course has improved. A number of clinical factors have been identified that predict CD progression including disease location, young age at diagnosis, disease behavior, perianal disease, use of steroids at diagnosis, and smoking. Some serological tests, such as antibodies against Saccaromyces cerevisae and genetic markers, have also been used in an effort to improve risk stratification. In 2014, the AGA published CD Clinical Care Pathway, which includes patient stratification according to their disease burden (Appendix E) [5]. Using this care pathway, patients are considered being at moderate-high risk for CD complications due to disease progression if they are <30 years of age at initial diagnosis, have extensive anatomic involvement, have perianal and/or severe rectal disease, have deep ulcers, or have had prior surgical resection and structuring and/or penetrating behavior. Siegel et al. created a web-based tool, the PROSPECT CD Risk Calculator, which has been used to predict outcomes and response to treatment for individuals [4,6]. This tool has been validated in pediatric and adult patients with CD. About 20% of patients with CD have an indolent course of disease from the time of diagnosis and are considered low risk for disease complications. Only subjects with suspected aggressive CD at increased risk for disease complications will be enrolled in the study.

As CD is a progressive disease with long-term structural complications, the proposed duration of this study is 102 weeks, in order to provide long-term efficacy data of vedolizumab maintenance therapy following triple combination induction therapy. Secondary endpoints will include achieving and maintaining clinical remission and maintaining endoscopic remission, and additional endpoints will include PROs and AEs. All subjects will receive vedolizumab IV 300 mg on Day 1, Weeks 2 and 6, and Q8W thereafter until Week 102; adalimumab 160 mg SC on Day 2, 80 mg SC at Week 2, and 40 mg SC every 2 weeks thereafter until Week 26; and oral methotrexate 15 mg weekly until Week 34. The initial dosing recommendations in the dosing regimen for both vedolizumab IV and adalimumab SC follow the approved labels [14,44].

If a subject has an exacerbation of CD after 26 weeks, defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, with objective evidence of disease activity by colonoscopy AND elevated CRP, OR fecal calprotectin >250 µg/g alone, then frequency of vedolizumab infusions will be changed to vedolizumab 300 mg IV Q4W, instead of vedolizumab 300 mg IV Q8W for the remainder treatment. Clinical remission and response rates increased in patients who lost response to Entyvio Q8W in GEMINI I and II when Entyvio dosing frequency was increased to Q4W in GEMINI long-term safety (LTS) study [45]. In CD, increased dosing frequency from every 8 weeks (GEMINI II) to every 4 weeks (GEMINI LTS) improved outcomes in patients who had withdrawn early from GEMINI II, with 47% experiencing clinical response and 32% in remission at Week 52 of GEMINI LTS, up from 39% and 4% before the dose increase. Analysis of real world data has similarly demonstrated that administration Q4W may help capture response in subjects who have lost response with dosing Q8W [46].

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the triple combination of vedolizumab, adalimumab, and methotrexate such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to enrollment. 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 non-pregnant, non-breast-feeding female and aged 18 to 65 years, inclusive at time of Screening.
4. The subject has an initial diagnosis of CD established within 24 months prior to Screening with involvement of the ileum and/or colon that can be assessed by ileocolonoscopy.
5. The subject has moderate to severely active CD during Screening defined by a centrally assessed SES-CD score ≥7 (or ≥4 if isolated ileal disease).
6. By investigator judgement, the subject is assessed as having CD at moderate-high risk for complications. Investigator judgement may include clinical assessment, the PROSPECT tool, or criteria defined by the 2014 AGA CD Clinical Care Pathway.
7. The subject may be receiving a stable therapeutic dose of conventional therapies for CD listed in the permitted medications and treatments below.
8. If the subject is on corticosteroids, they must be on a stable dose of oral corticosteroids up to 30 mg of prednisone daily or 9 mg of budesonide daily for at least 7 days prior to enrollment.
9. If the subject is on corticosteroids, they must be willing to follow a mandatory taper of prednisone or budesonide within 60 days after enrollment.
10. The subject must be willing to stop treatment with 5-aminosalicylate (5-ASA), antibiotics, and probiotics for luminal CD at enrollment.

11. [Previous criterion 11 deleted in amendment number 1].

12. 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.
13. 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 9.1.27 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.28 Pregnancy.

14. 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

The exclusion criteria are divided into 3 categories: GI exclusion criteria, infectious disease exclusion criteria, and general exclusion criteria. Subjects meeting any of the following criteria will not qualify for entry into the study:

7.2.1 Gastrointestinal Exclusion Criteria

1. The subject has a diagnosis of UC or indeterminate colitis.
2. *[Previous criterion 2 deleted in amendment number 1].*
3. The subject has clinical evidence of a current abdominal abscess or a history of prior abdominal abscess.
4. The subject has a known perianal fistula with abscess. (The subject may have a perianal fistula *without* abscess.)
5. The subject has a known fistula (other than perianal fistula).
6. The subject had non-CD related abdominal surgery within 6 months prior to enrollment.
7. The subject has any prior CD-related surgery OR CD complication requiring surgery at any time (other than seton placement for perianal fistula without abscess).
8. The subject has a history of 2 or more non-CD related small bowel resections or diagnosis of short bowel syndrome.
9. The subject has extensive non-CD related colonic resection, ie, subtotal or total colectomy with <15 cm colon remaining.
10. The subject has an ileostomy or colostomy.

11. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
12. The subject has a history or evidence of colonic mucosal dysplasia.
13. The subject has intolerance or contraindication to undergo ileocolonoscopy.
14. The subject has known fixed stricture or stenosis of the intestine.

7.2.2 Infectious Disease Exclusion Criteria

15. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection).
16. Subject has undergone organ transplantation.
17. The subject has evidence of an active infection during Screening.
18. Infections requiring treatment with oral (PO) or IV antibiotics, antivirals, or antifungals within 28 days of enrollment.
19. The subject has active or latent 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 QuantiFERON test 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)
20. The subject has a history of listeria, histoplasmosis, coccidioidomycosis, blastomycosis, candidiasis, aspergillosis, legionella, or pneumocystosis.
21. The subject has a history of any bacterial, viral, and other infection due to opportunistic pathogens.
22. The subject has chronic hepatitis B virus* (HBV) or hepatitis C virus (HCV) infection. *HBV immune subjects (ie, being hepatitis B surface antigen negative and hepatitis B surface antibody positive), may however, be included.
23. The subject has evidence of active *Clostridium difficile* infection or is having treatment for *C difficile* infection or other intestinal pathogens during Screening.
24. The subject has received any live vaccinations within 28 days prior to enrollment.

7.2.3 General Exclusion Criteria

25. The subject has other inflammatory or rheumatic diseases (eg, psoriasis, rheumatoid arthritis, ankylosing spondylitis).

26. The subject had a surgical procedure requiring general anesthesia within 60 days prior to enrollment or is planning to undergo major surgery during the study period.
27. The subject is required to take any excluded medications (as listed in Section 7.3).
28. The subject has received either approved or investigational biologic or nonbiologic agents for the treatment of IBD in an investigational protocol.
29. The subject has had prior exposure to any TNF antagonist including infliximab, certolizumab pegol, golimumab, adalimumab, or biosimilar TNF antagonist agents.
30. The subject has had prior exposure to approved or investigational anti-integrin antibodies (eg, vedolizumab, natalizumab, efalizumab, etrolizumab, AMG 181, anti-MAdCAM-1 antibodies, or rituximab).
31. The subject has received either approved or investigational biologic agents for the treatment of non-IBD conditions, other than localized injections (eg, intraocular injections for wet macular degeneration).
32. The subject has a history of hypersensitivity or allergies to methotrexate, vedolizumab, adalimumab, or their components.
33. The subject has a medical history that contraindicates the use of vedolizumab, adalimumab, or methotrexate as per each drug's package insert.
34. The subject has conditions which, in the opinion of the investigator, may interfere with the subject's ability to comply with the study procedures.
35. The subject has a history of any lymphoma or lymphoproliferative disease.
36. The subject has a history of congestive heart failure (New York Heart Association class III/IV) or unstable angina.
37. The subject has renal insufficiency, ascites, pleural effusion, or underlying liver disease.
38. 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.
39. The subject has had gastric bypass surgery.
40. The subject has symptoms of shortness of breath and cough and/or a diagnosis of clinically significant lung disease.
41. The subject has a history of malignancy, except for the following: adequately-treated nonmetastatic basal cell skin cancer; squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to Screening; and history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to Screening. Subjects with a remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of

the malignancy and the therapy received; this must be discussed with the sponsor on a case-by-case basis prior to enrollment.

42. The subject has a history of any major neurological disorders, including stroke, central nervous system demyelinating disease, brain tumor, or neurodegenerative disease.
43. The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist during Screening or prior to the administration of study drug on Day 1.
44. The subject has a history of pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia (WBC count $<3 \times 10^9$/L), thrombocytopenia (platelet count $<100 \times 10^9$/L), or significant anemia (hemoglobin level <8 g/dL).
45. The subject has rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
46. The subject has any of the following laboratory abnormalities during the Screening period:
    a) Hemoglobin level <8 g/dL.
    b) WBC count $<3 \times 10^9$/L.
    c) Lymphocyte count $<0.5 \times 10^9$/L.
    d) Platelet count $<100 \times 10^9$/L or $>1200 \times 10^9$/L.
    e) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 the upper limit of normal (ULN).
    f) Alkaline phosphatase >1.5 x ULN.
    g) Renal dysfunction (serum creatinine concentration greater than 1.5 mg per deciliter [133 µmol per liter]) or estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 at Screening

    Note: Retesting laboratory values during the screening interval may be considered with consultation from the Medical Monitor.
47. The subject has a history of high alcohol consumption (more than 7 drinks per week), a history of prior alcohol abuse within 5 years prior to enrollment, has alcoholic liver disease, has withdrawal symptoms, or a history of illicit drug use.
48. The subject has an active psychiatric problem that, in the investigator's opinion, may interfere with compliance with study procedures.
49. The subject is unable to attend all the study visits or comply with study procedures.
50. 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.
51. The subject's body mass index is >37.

52. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 6 months after participating in this study; or intending to donate ova during such time period.
53. If male, the subject intends to father a child or donate sperm during the course of this study or for 6 months thereafter.

7.3 Excluded Medications

The following medications are excluded from use during the study, from the time of informed consent to Week 102, unless specified otherwise:

- Any treatment for CD other than those listed below in Section 7.3.1 (either approved or investigational).
- Azathioprine and 6-mercaptopurine must be discontinued within 28 days prior to enrollment (Day 1).
- Investigational or noninvestigational nonbiologic therapies.
- Trimethoprim/sulfamethoxazole.
- Leflunomide.
- Theophylline.
- Tizanidine.
- Phenytoin, phenylbutazone, or probenecid.
- All live vaccines within 28 days prior to enrollment, 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).
- Oral corticosteroids for CD except as described in Section 7.3.1.1; 5-ASA or corticosteroid enemas/suppositories are to be discontinued prior to enrollment.
- Chronic nonsteroidal anti-inflammatory drug (NSAID) or salicylates use. (Note: Occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc, and daily use of baby or low-dose [81-162.5 mg] aspirin for cardiovascular prophylaxis are permitted.)
- Oral 5-ASA compounds, probiotics (eg, Culturelle, Saccharomyces boulardii), and antibiotics for luminal CD must be discontinued prior to enrollment.

Other medications may reduce the clearance of methotrexate. Subjects receiving the following additional medications during the study should be carefully monitored for increased side effects: penicillins, oral antibiotics (ciprofloxacin, tetracycline, chloramphenicol), nonabsorbable broad spectrum antibiotics, aminoglycosides, amphotericin B, and kanamycin.

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 corticosteroid therapy for CD with mandatory tapering completed by 60 days after study enrollment as described in Section 7.3.1.1.
- Antidiarrheals for control of chronic diarrhea.
- Systemic antibiotics for treatment of non-CD indications or perianal CD prior to or after seton placement are permitted for a maximum of 14 consecutive days.

Subjects will take folic acid as a companion medication through Week 34 (while taking methotrexate).

Subjects are permitted to have seton placement surgery for perianal fistula.

7.3.1.1 Oral Corticosteroid Dosing and Tapering

The maximum dose of oral corticosteroids for the treatment of CD that may be co-administered with vedolizumab IV is 30 mg/day prednisone or 9 mg/day budesonide (or equivalent) as long as the dose has been stable for at least 7 days prior to enrollment.

It is required that subjects receiving oral corticosteroids begin a tapering regimen by 14 days after enrollment and that the taper is completed within 60 days after enrollment. The recommended tapering schedule is as follows:

- For prednisone at doses >10 mg/day (or equivalent), the dose should be reduced at a rate of 5 mg/week until 5 mg/day is reached, and then the dose should be reduced at a rate of 2.5 mg/week until discontinuation.
- For prednisone at doses ≤10 mg/day (or equivalent) 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 2 weeks until discontinuation.

7.3.1.2 Medications for CD Exacerbation After 26 Weeks

If a subject has a first exacerbation of CD after 26 weeks as defined in the following paragraph, then the frequency of vedolizumab infusions will be changed to vedolizumab 300 mg IV Q4W, instead of vedolizumab 300 mg IV Q8W, for the remainder treatment to Week 102.

A first exacerbation of CD after 26 weeks is defined as either:

- A CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, OR
- Objective evidence of disease activity by colonoscopy and CRP above normal, OR
- Fecal calprotectin >250 µg/g alone.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.29.

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

   - LFT Abnormalities

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

   - Leukopenia or Lymphopenia. WBC and lymphocyte counts will be monitored for all subjects. Methotrexate, if applicable, should be discontinued and the dose of study drug held for an absolute lymphocyte count <0.5 × 109/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of study drug can be administered only if the absolute lymphocyte count is ≥0.5 × 109/L. If the absolute lymphocyte count remains <0.5 × 109/L, study drug should be discontinued and the subject withdrawn from the study.

2. Subjects who require surgical intervention for the treatment of CD except for seton placement for perianal fistula without abscess.
3. Significant protocol deviation. The discovery postenrollment that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and/or continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

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

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.28.
8. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment (including the CD worsening criteria listed below) and continued participation would pose an unacceptable risk to the subject.
   - Subjects with CD worsening during the first 26 weeks defined as ≥100-point increase in CDAI score since Screening that occurs after Week 10 on 2 consecutive visits and a CDAI score ≥220 points ***OR***
   - Subjects with a second exacerbation of CD after Week 26 defined as a >70-point increase in CDAI score from the prior visit on 2 consecutive visits separated by a 2-week interval and CRP above normal, or defined as fecal calprotectin >250 µg/g alone.
9. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.3.1.2. 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 the long-term follow-up (LTFU) phone call at 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 Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Vedolizumab IV

The study sites will be supplied by the sponsor with the following medication in an open-label manner: vedolizumab IV 300 mg/vial, for single use, in 20 mL vials. The study medication will be provided in a glass vial as a lyophilized solid 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.

All infusions will be administered IV over approximately 30 minutes. Longer infusion times of up to 60 minutes may be used based on subject observations. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion in a room where appropriate treatment for infusion-related reactions is available. The subject should be considered clinically stable by the investigator or designee prior to discharge.

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

8.1.1.2 Adalimumab SC

The study sites will be supplied by the sponsor with the following medication in an open-label manner: adalimumab 40 mg in prefilled syringes. Adalimumab will be supplied in a clinical carton containing 1 prefilled syringe. The clinical carton and each prefilled syringe will be labeled with a single-panel or multilingual booklet label that will contain, but will not be limited to, the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, caution statement, directions for use, and storage conditions.

Additional reference information and administration instructions can be found in the pharmacy manual and Instructions for Use for study participants.

8.1.1.3 Oral Methotrexate

The study sites will be supplied by the sponsor with the following medication in an open-label manner: methotrexate 2.5 mg tablets in a 100-count bottle. The subject will take six 2.5 mg tablets (for a total dose of 15 mg) at 1 time.

Methotrexate will be supplied in the manufacturer's original bottle. Each bottle will be appropriately labeled with a single-panel or multilingual booklet label that will contain, but will not be limited to the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, caution statement, directions for use, and storage conditions.

Additional reference information and administration instructions can be found in the pharmacy manual and Instructions for Use for study participants.

8.1.2 Storage

Investigational drugs must be kept in an appropriate, limited-access, secure place until they are used or returned to the sponsor or designee for destruction. Investigational drugs must be stored under the conditions specified on the labels, and remain in the original containers until dispensed. A daily temperature log of the drug storage area must be maintained.

Vedolizumab IV must be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze. Do not use if frozen even if the drug has been thawed.

Adalimumab must be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). It should be kept in its original container and protected from light until administered. Do not freeze. Do not use if frozen even if it has been thawed.

Oral methotrexate tablets must be stored at room temperature between 20°C and 25°C (68°F and 77°F) with excursions permitted to 15°C to 30°C (59°F-86°F). The tablets should be stored in the packaging provided, which prevents access of moisture and provides protection from light.

8.1.3 Dose and Regimen

The dose and regimen for all subjects is provided in Table 8.a.

Vedolizumab infusion will take place at the study center and be administered intravenously over 30 minutes. Instructions for reconstitution and 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.

Adalimumab SC will be administered at the clinical site on Day 1 (160 mg/mL). The subject should return to the site the day after (or within a 3-day window of) the vedolizumab infusion to self-administer the adalimumab SC injection while instructed and observed by site staff or to have the injection administered by qualified site staff. Subsequent doses (80 mg/mL and then 40 mg/mL) will be self-administered at home starting at Week 2. Weeks 2, 6, 14, and 22 adalimumab will be administered 1 day after the vedolizumab infusion. Additional reference information and administration instructions can be found in the pharmacy manual and Instructions for Use for study participants.

Methotrexate will be taken weekly on the same day each week in the form of six 2.5 mg tablets (for a total dose of 15 mg). Subjects must take a daily folic acid supplement (1 mg PO) during the 34 weeks of methotrexate treatment.

When adalimumab and vedolizumab are due to be given to a subject on the same day, the vedolizumab infusion should be given as scheduled at the study center and then the subject should self-administer the adalimumab SC injection at home the next day.

If a subject has a first exacerbation of CD after 26 weeks, defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, OR objective evidence of disease activity by colonoscopy and CRP above normal, OR fecal calprotectin >250 µg/g alone, then frequency of vedolizumab infusions will be changed to vedolizumab 300 mg IV Q4W, instead of vedolizumab 300 mg IV Q8W for the remainder treatment.

Table 8.a Dose and Regimen

Treatment Phase	Dose	Treatment Description
Triple Combination Therapy	Vedolizumab 300 mg IV	IV infusion with vedolizumab at Weeks 0, 2, 6, 14, and 22.
	Adalimumab (a) 160 mg (4 x 40 mg), 80 (2 x 40 mg), 40 mg SC	Induction: 160 mg at Week 0, 80 mg at Week 2, 40 mg at Week 4 and every 2 weeks after until Week 26.
	Methotrexate 15 mg PO	15 mg PO weekly from Weeks 0 to Week 34 (with folic acid supplement taken during this period).
Monotherapy	Vedolizumab 300 mg IV	IV infusion with vedolizumab at Weeks 30, 38, 46, 54, 62, 70, 78, 86, 94, and 102. (Subjects with a first exacerbation of CD after 26 weeks will receive vedolizumab 300 mg IV every 4 weeks following the exacerbation. Please refer to the Schedule of Study Procedures in Appendix A for dosing schedule.)

Abbreviations: CD, Crohn's disease; IV, intervenous; PO, oral.
(a) At Weeks 0, 2, 6, 14, and 22, adalimumab will be administered 1 day after the vedolizumab infusion. For Week 0, the subject should return to the site the day after (or within a 3-day window of) the vedolizumab infusion to self-administer the adalimumab SC injection while instructed and observed by site staff or to have the injection administered by qualified site staff. Subsequent doses will be self-administered at home starting at Week 2.

8.1.4 Overdose

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

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

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to study schedule.

The investigator or investigator's designee will access the interactive response technology (IRT) at screening to obtain the subject study number. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening.

The medication identification number (Med ID) of the investigational drug to be dispensed will then be provided by the IRT by email notification to the site pharmacist/nurse. If sponsor-supplied drug (vials or prefilled syringes) is lost or damaged, the site staff can request a replacement from the IRT.

Refer to the IRT manual provided separately. At subsequent drug-dispensing visits, the investigator or designee will again contact the IRT to request additional investigational drug for a subject.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator and investigator's designated site pharmacy must ensure that the sponsor- or contract research organization (CRO)-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of the sponsor-supplied drugs (vedolizumab IV, adalimumab prefilled syringes, and methotrexate tablets), the investigator pharmacy/site must maintain records of drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee. The use of the CRO-supplied supplement (folic acid) must be documented in the subject's medical record.

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 IRT. 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 IRT).
- 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 IRT 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 the sponsor-supplied drugs (vedolizumab IV, adalimumab prefilled syringes, and methotrexate tablets) 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 the 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.

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.

Investigator sites that have the ability to destroy Investigational Product /Materials locally (not returned to Sponsor or it's designee for destruction), must have an SOP governing IP destruction and provide a copy of the SOP to the Sponsor/Sponsor Representative for review and approval. The site must provide a certificate of destruction for all IP/materials destroyed on-site. If the site does not have a certificate of destruction form they can use the form that is available in the IRT system. A file-note should be written stating that IP/materials was destroyed in compliance with the site SOP, and the file-note should be attached to the site IP accountability logs for verification and reconciliation.

If an Investigator site is not able to store their Investigational Product/Materials until the site CRA has performed verification and reconciliation, then the site must provide a copy of the governing SOP to the Sponsor/Sponsor representative for approval. If an Investigator site is utilizing an electronic system to manage IP/materials, they must provide evidence that the system is 21 CFR PART 11 compliant. Investigator designated site Pharmacists must be delegated duties on the site Delegation of Authority log.

8.4 Companion Medication

Treatment with folic acid is required from enrollment/Day 1 though Week 34 (while taking methotrexate). Subjects will take a single 1-mg capsule or tablet PO daily per the investigator's instruction. Folic acid will be provided by the CRO/Site.

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 IRT system; this subject number will be used throughout the study.

Pharmacogenomic (PGx) informed consent is a component of the overall study informed consent. The requirements are described in Section 15.2. Subjects will have the capability to opt out of the PGx component of the informed consent, if requested.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity (as applicable), race as described by the subject, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8.)

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 30 days prior to signing of informed consent. Medication history should be captured on the Medication History/Concomitant Medications eCRF page.

In addition, a history of all prior biologic use and any medications taken for the treatment of CD, including the reason for discontinuation, that stopped at or prior to signing of informed consent, is to be collected at screening for subjects where possible. Any prior CD treatment should be captured on the Prior CD Treatment eCRF only, and CD treatment started after signing informed consent, should be captured on the Concomitant Medications eCRF page only.

9.1.3 Crohn's Disease History

CD history collected at screening will include details of CD diagnosis, disease severity, surgery, hospitalizations, and extraintestinal manifestations. After signing of informed consent all subjects should have CD included on the Concurrent Medical Condition eCRF page.

9.1.4 Physical Examination Procedure

A 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 (oral or tympanic measurement), respiratory rate, blood pressure (resting more than 5 minutes), and pulse (resting more than 5 minutes).

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, as described in the Risk Assessment and Minimization for PML (RAMP) algorithm referenced in Section 11.1.1. The symptoms from a positive PML checklist obtained after enrollment will be recorded as an AE. Additional information and tools for the RAMP can be found in the Reference Binder.

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 investigational site) will interpret the ECG using one 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 Predicting CD Disease Course

The investigator will assess whether the subject has CD at moderate-high risk for complications. Investigator judgement may include clinical assessment, the PROSPECT tool, or criteria defined by the 2014 AGA CD Clinical Care Pathway [4-6].

9.1.10.1 Investigator clinical assessment

Clinical criteria that predict CD progression and complications include:

- Involvement of the upper GI tract and/or ileum,
- Young age at diagnosis,

- Penetrating CD behavior (Subjects with a known non-perianal fistula are however excluded from this study),
- Perianal disease,
- Use of steroids at diagnosis,
- Smoking.

9.1.10.2 AGA CD Clinical Care Pathway

Using the AGA 2014 Clinical Care Pathway [5], patients may be assessed as moderate-high risk for CD complications due to disease progression using the following criteria:

- <30 years of age at initial diagnosis,
- Extensive anatomic involvement,
- Perianal or severe rectal disease,
- Deep ulcers,
- Prior surgical resection or stricturing and/or penetrating behavior.

9.1.10.3 PROSPECT CD Tool

The PROSPECT CD Risk Calculator is a web-based tool used to predict outcomes and response to treatment [4,6]. For subjects whom the investigator chooses to implement the PROSPECT tool, their blood will be drawn at the time of informed consent and shipped to Prometheus Labs, San Diego, CA (or other lab) for serologic and genetic markers. If an investigator chooses not to utilize the PROSPECT tool to assess a subject's risk of developing CD complications, blood may still be collected for serologic and genetic markers for the endpoint analysis of PROSPECT tool performance at any time during the subject's screening period. Further instruction on the collection and handling of these samples can be found in the study Laboratory Manual. The results of these tests will be used as inputs to the PROSPECT predictive tool. This mathematical prediction tool incorporates basic disease characteristics including disease location and time since diagnosis, in addition to serologic markers such as anti-*Saccharomyces cerevisiae* antibody (ASCA), CBir, perinuclear antineutrophil antibody (pANCA), and a single genetic polymorphism of NOD2. The results of the serologic and genetic markers will be sent to the PROSPECT coordinator who will input the results to create an output graphical representation of that individual's risk with ≥20% chance of disease complication by Year 2. These results will be then sent to the site investigator to be considered as part of the investigator's assessment of a subject's risk of CD complications.

9.1.10.4 Monitr Crohn's Disease Test

The Monitr Crohn's Disease Test is a laboratory-developed test from Prometheus Labs that evaluates multiple markers of mucosal damage and repair processes, regardless of disease location. It applies a proprietary algorithm to 13 biomarkers to produce a quantitative Endoscopic

Healing Index Score, ranging from 0 to 100, to aid in distinguishing endoscopic remission from active disease in adult CD patients [47].

A blood sample for Monitr CD will be collected at Week 26 and Week 102 or early termination.

In addition, Baseline Week 0, Week 26 and Week 102 samples may be analyzed for subjects who have already completed those visits prior to Amendment #4. After PK and Immunogenicity testing are completed, any residual frozen serum aliquots from PK and/or Immunogenicity testing may be repurposed for this testing. These samples will only be used after receiving subject consent/reconsent.

Further instruction on the collection and handling of these samples can be found in the study Laboratory Manual.

9.1.11 Colonoscopy and Biopsy Procedure

Colonoscopy will be performed during screening and at Weeks 26 and 102 or early termination. All study colonoscopies will be video-recorded using the Robarts Central Image Management Solution (CIMS). All study endoscopy videos will be subject to central review to ensure consistent grading. A central reviewer will confirm the SES-CD inclusion criterion prior to subject enrollment. Central reviewer's grading will stand as final assessment for eligibility. CIMS will communicate incidental findings observed during central review to the investigator/study team for additional follow up.

At each colonoscopy, up to 4 biopsies for histopathology will be collected from 5 segments (for a total of up to 20 biopsies): the rectum, left colon, transverse colon, right colon, and ileum. Biopsies will be taken in the vicinity of the most prominent ulcerative lesions, if present. If there is more than 1 area of inflammation within a segment, 2 biopsies should be taken from the most severely affected area of inflammation and 2 biopsies should be taken from the normal mucosa adjacent to this area of inflammation. For each colonic segment, biopsies from inflamed and normal mucosa should be placed in separate specimen containers. In those instances in which the mucosa of an entire segment appears normal, 2 biopsies should be taken from normal mucosa. Additionally, if the mucosa of an entire segment is inflamed, 2 biopsies should be obtained from the most severely affected area of inflammation.

The site of the biopsy collection will be recorded. Work Instructions will detail the requirements for study colonoscopy and biopsy. Subject preparation for colonoscopy should follow the site's usual clinical practice (such as polyethylene glycol).

All biopsies collected per protocol will be centrally stored and analyzed at the end of the study. Although it is permissible for the investigator to take additional biopsy samples as deemed necessary for standard of care management of the patient during the protocol-required colonoscopy, these will be considered as occurring outside the protocol. Such collection, handling, and analyses of the additional samples will be and remain the responsibility of the investigator.

9.1.12 Primary Efficacy Measurement

The primary efficacy measure is the percentage of subjects who achieve endoscopic remission, defined as SES-CD 0-2 at Week 26.

9.1.13 The SES-CD

The SES-CD [48] evaluates 4 endoscopic variables (ulcer size, proportion of the surface area that is ulcerated, proportion of the surface area affected, and stenosis) by scoring each variable on a scale from 0 to 3 where higher scores indicate more severe disease, in 5 bowel segments (ileum, right colon, transverse colon, left colon, and rectum).

The score for each endoscopic variable is the sum of the values obtained for each segment. The SES-CD Total is the sum of the 4 endoscopic variable scores from 0 to 56. See Appendix F.

9.1.14 CDAI

A CDAI [49] score will be calculated at baseline Week 0, using subject diary entries during screening within 14 days prior to enrollment, and is based on the most recent 7 days with complete and valid data within a maximum consecutive 10 day period. Note that diary entries on the day prior, day of, and the day after the colonoscopy cannot be used for CDAI sub-score calculation. For the baseline CDAI the hematocrit results collected during screening should be used. 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 G. A Standard Weight Table is provided in Appendix H.

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. Entries should be reviewed and monitored by the study staff.

9.1.16 PRO-2

A 2-item patient-reported outcome, PRO-2, will be derived from 2 elements of the CDAI diary (stool frequency and abdominal pain) from the 7 days prior to score calculation [50]. See Appendix I.

9.1.17 Additional Patient-Reported Outcome Measures

Subjects will complete the IBDQ, WPAI-CD, and the IBD-DI at the time points specified in the schedule of events (Appendix A).

9.1.17.1 Inflammatory Bowel Disease Questionnaire

The IBDQ is a valid and reliable [51-53] instrument used to assess HRQOL 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 J.

9.1.17.2 Work Productivity and Activity Impairment - Crohn's Disease

The WPAI-CD consists of 6 questions that evaluate absenteeism (work time missed), presenteeism (reduced work productivity), overall work impairment, and activity impairment [54,55]. The WPAI-CD questionnaire will be self-administered by the study subjects.

9.1.17.3 Inflammatory Bowel Disease - Disability Index

The IBD-DI is the first specific instrument for evaluating disability in IBD. It is based on core sections of the World Health Organization's International Classification of Functioning, Disability, and Health and was designed to evaluate the long-term effects of IBD on subject functional status and to provide a new endpoint in disease-modification studies [56]. The IBD-DI consists of 14 questions that focus on body functions, body structures, activities and participation, and environmental factors. Scores range between 0 to 100, with 0 to 20 indicating no disability, 20 to 35 mild disability, 35 to 50 moderate disability, and 50 to 100 severe disability. The IBD-DI recently has been validated for use in clinical trials, including results from 150 subjects with CD, having shown high internal consistency, interobserver reliability, and construct validity, as well as moderate intraobserver reliability [57].

9.1.18 Documentation of Concomitant Procedures

At each visit, subjects will be asked whether they have had any CD-related events since their last visit including hospitalizations, bowel surgeries, or CD-related procedures that are not part of the protocol. The timing of the event will be collected relative to the start of treatment on Day 1 of the study through the last clinic visit (Week 120). All events with timing will be recorded in the eCRFs. The underlying symptom or diagnosis should correspondingly be recorded as an AE as applicable.

9.1.19 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the required study medication (methotrexate, vedolizumab, adalimumab, or the companion folate). These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study-specified medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Concomitant medication information will be collected through Week 120 (18 weeks post last dose).

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 45 mL, and the approximate total volume of blood for the study is 476 mL. Details of these procedures, specimen handling and required safety monitoring will be given in the laboratory manual.

Table 9.a Clinical Laboratory Tests

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

Other:	
HIV	ASCA IgA
Hepatitis panel, including HBsAg and anti-HCV	ASCA IgG
	Anti-CBir1 IgG
	ANCA
	NOD2 genotype test

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Serum	**Urine**	**Stool**
CRP PK samples ADA/nADA QuantiFERON for TB beta hCG (for pregnancy in female subjects of childbearing potential only) FSH, if menopause is suspected (screening visit only) Monitr CD Test (biomarker panel using serum to measure hsCRP, SAA 1, CEACAM 1, VCAM 1, ANG 1, ANG 2, IL-7, TGFα, EMMPRIN, MMP 1, MMP 2, MMP 3, and MMP 9)	hCG (for pregnancy in female subjects of childbearing potential only)	Fecal calprotectin *C difficile* (b)

Abbreviations: ADA,antidrug antibodies; ALT, alanine aminotransferase; ASCA, anti-*Saccharomyces cerevisiae* antibody; AST, aspartate aminotransferace; anti-CBir1, anti-flagellin; CRP, C-reactive protein; FSH, follicle-stimulating hormone;GGT, γ-glutamyl transferase; HBsAg, hepatitis B surface antigen; hCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ANCA, antineutrophil antibody; IgA, immunoglobulin A; IgG, immunoglobulin G; nADA, neutralizing antidrug antibodies; NOD2, nucleotide-binding oligomerization domain-containing protein; PK, pharmacokinetic; PT, prothrombin time; RBCs, red blood cells; TB, tuberculous; WBC, white blood cell; ULN, upper limit of normal; hsCRP, high-sensitivity C-reactive protein; SAA 1, serum amyloid A 1; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1: VCAM 1, vascular cell adhesion molecule 1; IL-7, interleukin-7; TGFα, transforming growth factor α; EMMPRIN, extracellular matrix metalloproteinase inducer; MMP, matrix metalloproteinase

(a) WBC differential to include lymphocytes, monocytes, basophils, eosinophils, and neutrophils.

(b) Not done at screening; only done if subject experiences a flare during the study.

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, γ-glutamyl transferase (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 7.3.1.2 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

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

9.1.21 Fecal Calprotectin Sample Collection

A stool sample will be collected from the first bowel movement in the morning at the time points indicated in the Schedule of Study Procedures (Appendix A) for the analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity. Sites are encouraged to provide subjects with a stool sample kit at the time of clinic visits. Stool samples may be stored in the refrigerator at 4°C and should be returned to the clinic within 48 hours of collection.

9.1.22 Stool Sample Collection

A stool sample will be obtained to perform a *C difficile* assay at any point in the study when a subject becomes symptomatic, including worsening or return of disease activity.

9.1.23 Pharmacokinetic Sample Collection

Vedolizumab - Blood samples (5 mL) will be drawn for vedolizumab serum PK analysis in all subjects on Day 1 and at the time points indicated in the Schedule of Study Procedures (Appendix A). Blood samples should be drawn prior to start of infusion at visits where study drug is given.

Adalimumab - Blood samples (5 mL) will be drawn for adalimumab serum PK analysis in all subjects on the same day as the visit and prior to vedolizumab dosing on Day 1 and at the time points indicated in the Schedule of Study Procedures (Appendix A).

At time points where both vedolizumab and adalimumab require blood samples, separate samples will be drawn for each drug.

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.

Serum concentrations adalimumab will be measured by a sandwich ELISA assay with a validated range of 0.25 to 10.0 µg/mL.

Samples collected outside that window will not be considered protocol deviations as long as they are collected prior to vedolizumab dosing, and the dosing and sampling dates and times are accurately collected in the eCRF.

It is important that the EXACT date and time of dosing (start and end of infusion for vedolizumab) and PK sampling for both drugs be recorded in the eCRF.

Detailed instructions for the handling and shipping of samples are provided in Appendix K.

9.1.24 Anti-Drug Antibodies Sampling

Blood samples for ADA assessments for vedolizumab will be obtained on Day 1 prior to dosing at the time points indicated in the Schedule of Study Procedures (Appendix A).

Blood samples for ADA assessments for adalimumab will be obtained on Day 1 prior to vedolizumab dosing at the time points indicated in the Schedule of Study Procedures (Appendix A).

Serum titers of ADA to vedolizumab and adalimumab will be determined using a validated assay. A separate assay will be required for each drug. nADAs to vedolizumab will be determined on ADA-positive samples using a validated assay. nADAs to adalimumab will only be determined if deemed necessary for the interpretation of the data.

Please refer to the Reference Binder for information on sample collection and preparation.

9.1.25 Pharmacogenomic Sampling

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

Two whole blood samples (3 mL per sample) for DNA isolation will be collected before dosing on Day 1 from each subject in the study, into plastic K_2EDTA spray-coated tubes, and stored under frozen conditions. If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

Two whole blood RNA samples (2.5 mL per sample) for RNA PGx analysis will be collected on Day 1 from each subject in the study, into a PaxGeneTM tube. If DNA or RNA samples are not obtained on Day 1, they may be collected at any point in the study. Please refer to the Reference Binder for information on sample collection and preparation.

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

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

This information may be used, for example, to develop a better understanding of the safety and efficacy of vedolizumab and other study medications, and for improving the efficiency, design and study methods of future research studies.

The samples will be stored for no longer than 15 years after completion of the study. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. "Stored samples" are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drugs.

Detailed instructions for the handling and shipping of samples will be provided by the central laboratory in the laboratory manual.

9.1.26 Tuberculosis Screening

All subjects will complete TB screening to determine eligibility. All subjects must complete either a QuantiFERON test or a tuberculin skin test within 30 days of Screening or during Screening. Chest X-ray should be completed if high risk for TB or indeterminate skin test or QuantiFERON. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history.

9.1.27 Contraception and Pregnancy Avoidance Procedure

9.1.27.1 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 medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.27.2 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 medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from list below). In addition, they must be advised not to donate ova during this period.

9.1.27.3 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 (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) 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 postbilateral 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, alone or in combination, that 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:
   - Nonhormonal Methods:
     - Intrauterine device (IUD).
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
     - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 18 weeks after last dose.
   - Hormonal methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method.
     - 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 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 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, postovulation methods).
   - Spermicides only.

- Withdrawal.
- No method at all.
- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.

3. Subjects will be provided with information on highly effective/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 female partners of childbearing potential.
   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 as close as possible and prior to receiving any dose of Lead-in medication (ie, standard of care) and study medication and at the Week 102/End of Treatment Visit and Week 120/ Safety Follow-up Visit.

Methotrexate is in Pregnancy Category X. Methotrexate is contraindicated in pregnant women as it can cause fetal death or teratogenic effects. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and pregnancy should be avoided if either partner is receiving methotrexate.

9.1.27.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the recommendations previously described in Section 9.1.27.3, Item 4.

9.1.28 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and vedolizumab, adalimumab, and methotrexate should be immediately discontinued. The subject will be withdrawn as per the procedures in Section 5. In addition, any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after Visit 1 or within 18 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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 the open label treatment the subject received.

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

9.1.29 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 IRT 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.

9.1.30 Documentation of Study Entrance

Enrollment will be performed through the IRT system. Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance (enrollment) into the treatment phase.

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

9.2 Monitoring Subject Treatment Compliance

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.

An adalimumab and methotrexate dispensing log, including records of drug received from the sponsor and drug dispensed for home administration to each subject and returned by each subject, will be maintained by site.

If a subject is persistently noncompliant with the study medication, 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 enrollment. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. Subjects may be enrolled at any time during the screening period provided that all screening procedures have been completed and eligibility has been confirmed. See Section 9.1.29 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 Enrollment (Day 1) (Visit 2)

Enrollment of eligible subjects 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, the subject should be enrolled using the IRT as described in Section 8.2. Subjects will be given instructions for the first doses of triple combination therapy as described in Section 8.1.3. The procedure for documenting screening failures is provided in Section 9.1.29.

9.3.3 Week 102 or Final Treatment Visit (Visit 19)

The final treatment visit will be performed at Week 102 (Visit 19) (see Appendix A).

9.3.4 Week 120 or End-of-Study Visit (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 (Visit 20) will be scheduled for final efficacy and safety

assessments (Appendix A). For all subjects enrolled, the investigator must complete the End of Study Drug and End of Study Visits eCRF pages.

9.3.5 Poststudy Long-term Follow-up (26 Weeks Post-Treatment)

Upon completion of the study or at early termination from the study, all subjects will participate in a 26-week (6-month) LTFU safety questionnaire. This questionnaire will be administered at 26 weeks (6 months) from the last dose of study drug. The questionnaire will be administered via direct subject contact through either the study site or the designated study call center.

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:

- Symptom-directed physical examination.
- Vital signs assessment.
- Recording of concomitant mediations.
- Collection of AEs and SAEs.
- Clinical chemistry, CRP, and hematology, as indicated.
- Stool sample collection, including stool for *C difficile* and fecal calprotectin, if indicated.
- Fistula assessment, if indicated.
- CDAI.
- ADA sample.
- Colonoscopy, if indicated.

If a subject has a first exacerbation of CD after 26 weeks as defined in the following paragraph, then the frequency of vedolizumab infusions will be changed to vedolizumab 300 mg IV Q4W, instead of vedolizumab 300 mg IV Q8W, for the remainder of treatment to Week 102.

A first exacerbation of CD after 26 weeks is defined as either:

- A CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, OR
- Objective evidence of disease activity by colonoscopy and CRP above normal, OR
- Fecal calprotectin >250 µg/g alone.

9.3.7 Poststudy Care

Vedolizumab IV, adalimumab SC, and methotrexate 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 a commercial supply of vedolizumab, if approved in their country, at the discretion of their physician.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.25. The genetic material will be preserved and retained for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided PGx samples can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

In this study, ileocolonoscopy tissue samples will be preserved and retained for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The tissue samples will be sent to a central laboratory that serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided ileocolonoscopy tissue samples can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS, ADVERSE EVENTS, AND PRODUCT COMPLAINTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 PCs

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

An investigator who is made aware of or identifies a potential PC should immediately report the event to Takeda in accordance with the contact list provided to the site. Whenever possible, the associated product should be maintained in accordance with the instructions pending further guidance from a Takeda representative.

10.1.4 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.5 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).

10.1.6 Special Interest AEs

An AESI (serious or nonserious) 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 vedolizumab 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.

Injection and/or Infusion Site Reactions and Hypersensitivity

Currently, there is no evidence to support the routine prophylactic administration of premedication (eg, antihistamines, corticosteroids) to subjects receiving vedolizumab; hence, such premedications are unlikely to be necessary or beneficial. At the discretion of the investigator,

however, subjects may be administered premedication prior to any study drug administration. Corticosteroids, if given as a premedication, should be limited to the day of administration.

Study drugs 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 of vedolizumab.

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

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 changes in WBC, hemoglobin, and platelets 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 7.3.1.2.

Malignancies

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.

10.1.7 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.8 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.9 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.

10.1.10 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.

10.1.11 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.

10.1.12 Frequency

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

10.1.13 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.

- Not Applicable – a study medication was stopped for a reason other than the particular AE (eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE).
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.14 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 medication (Day 1; Visit 2) or until screen failure. For subjects who discontinue prior to study medication 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 medication (Day 1; Visit 2). Any drugs provided by the sponsor are considered study medications.

End of AE collection:

Routine collection of AEs will continue until the end-of-study follow-up (Week 120; Visit 20).

10.2.1.2 PTE and AE Reporting

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

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

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

CDAI 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 these instruments, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 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 10.1.6, 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 medication(s).
- Causality assessment.

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

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

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

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×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, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

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

11.1 Adjudication Committee

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

11.1.1 Risk 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 subjects who are immunocompromised [58,59]. Natalizumab is a pan- α4 integrin antagonist that binds to both the α4β1 and α4β7 integrins and inhibits cellular adhesion to vascular cell adhesion molecule-1 (VCAM-1) and MAdCAM-1 [60,61]. In contrast, vedolizumab binds to the α4β7 integrin only [11] and inhibits adhesion to MAdCAM-1, but not VCAM-1. A risk of PML cannot be ruled out with vedolizumab.

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 Reference Binder.

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 Reference Binder. 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 eCRFs

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 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.

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

12.2 Record Retention

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

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to data analyses. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to commencing analysis. 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 medication and have a postenrollment efficacy assessment will be included in the full analysis set (FAS). The FAS population will be used for the efficacy analysis and constitutes the primary analysis population for efficacy.

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 commencement of analysis 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 (SAF). All subjects who received at least 1 dose of study drug will be included in the SAF 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 Efficacy Analysis

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

The primary efficacy endpoint for this study is the percentage of subjects who achieve endoscopic remission, defined as SES-CD 0-2 at Week 26.

Secondary endpoints include the percentage of subjects who maintain endoscopic remission at Weeks 52 and 102 in subjects who achieved endoscopic remission at Week 26.

For all dichotomous endpoints (having achieved endoscopic remission at Week 26 and those maintaining deep remission at Weeks 52, 78, and 102), corresponding percentages and their appropriate 95% CIs will be reported. Time-to-event endpoints will be analyzed by survival analysis procedures and percentages will be estimated by Kaplan-Meier product limit methods and presented with appropriate 95% CIs.

Change from baseline in CDAI and PRO-2 scores will be analyzed using Wilcoxon signed-rank test for paired data; the median change and its nonparametric 95% CI will also be presented.

13.1.4 PK Analysis

Serum concentrations of vedolizumab and adalimumab will be summarized by time using descriptive statistics. Individual serum concentration data versus time will be presented in a data listing. Additional PK analyses may be performed if deemed necessary for the interpretation of the data.

More details will be provided in the SAP.

13.1.5 Anti-Drug Antibodies Analysis

Immunogenicity will be summarized by time and by treatment.

The percentage of subjects with positive ADA and the percentage of ADA positive subjects with positive nADA during the study will be summarized (anti-vedolizumab only). The impact of ADA on efficacy and safety will be explored.

13.1.6 Safety Analysis

Safety analyses will be based on the SAF analysis set.

No formal statistical tests or inference will be performed for safety analyses.

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 severity, and by relationship to study drug. If a subject experienced more than 1 AE for a given preferred term, severity is defined as the severity 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. 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

Additional details regarding any further analyses will be specified in detail in the SAP.

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis will be conducted once all subjects have completed their Week 26 study visit, in order to assess the primary endpoint.

13.3 Determination of Sample Size

The sample size was based on an estimate of precision. A sample size of 60 subjects will generate 95% CIs for endoscopic remission (defined as SES-CD 0-2) rate at Week 26 with a half width no wider than 12.7% and expected remission of 50%. If the expected remission rate is different from 50%, a required sample size would be smaller.

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

14.2 Protocol Deviations

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

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom

Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

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

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

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures

Induction Phase (Screening Through Week 26)											
	Screening	Treatment									
Study Week		Wk 0	Wk 2	Wk 4 (r)	Wk 6	Wk 8 (r)	Wk 10	Wk 14	Wk 18 (r)	Wk 22	Wk 26
Study Day ± Visit Window (Days)	Day -28 to Day -1	1	15 ±3	n/a	43 ±3	n/a	71 ±3	99 ±3	n/a	155 ±7	183 ±7
Visit Number:	1	2	3	n/a	4	n/a	5	6	n/a	7	8
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demographics/medical and medication history/ concurrent medical conditions	X										
CD History	X										
Physical examination	X	X	X		X		X	X		X	X
Vital signs (a)	X	X	X		X		X	X		X	X
Access IRT to obtain subject ID	X										
Access IRT to register visit		X	X		X			X		X	X
ASCA IgA, ASCA IgG, Anti-CBir1 IgG, ANCA, NOD2 genotype test	X										
CDAI		X	X		X		X	X		X	X
PRO-2	X	X									X
Ileocolonoscopy (b)	X										X
SES-CD	X										X
CRP	X	X					X				X
Fecal calprotectin (c)	X						X	X			X
Tuberculosis QuantiFERON or skin test (d)	X										
Chemistry, Hematology, Urinalysis	X	X	X		X		X	X		X	X
Hepatitis, HIV	X										

Induction Phase (Screening Through Week 26)											
	Screening	Treatment									
Study Week		Wk 0	Wk 2	Wk 4 (r)	Wk 6	Wk 8 (r)	Wk 10	Wk 14	Wk 18 (r)	Wk 22	Wk 26
Study Day ± Visit Window (Days)	Day -28 to Day -1	1	15 ±3	n/a	43 ±3	n/a	71 ±3	99 ±3	n/a	155 ±7	183 ±7
Visit Number:	1	2	3	n/a	4	n/a	5	6	n/a	7	8
Pharmacogenomic DNA and RNA samples (f)		X									
PK samples for vedolizumab (g)		X			X		X	X			X
PK samples for adalimumab (h)		X			X		X	X		X	X
ADAs samples, vedolizumab		X			X			X			X
ADAs samples, adalimumab		X	X		X		X	X		X	X
Pregnancy test (hCG) (i)	X										
Urine pregnancy test (i)		X	X		X		X	X		X	X
Home pregnancy test (j)									X		
ECG	X										
Vedolizumab (IV) (k)		X	X		X			X		X	
Adalimumab (SC) (l)		X (m)	X (m)	X	X (m)	X	X	X (m)	X	X (m)	X
Methotrexate (PO) (n)		X	X	X	X	X	X	X	X	X	X
Folic acid (PO) (o)		X	X	X	X	X	X	X	X	X	X
AE/SAE assessment		X	X		X		X	X		X	X
Concomitant medications/ procedures	X	X	X		X		X	X		X	X
PML checklist (p)	X	X	X		X			X		X	
PML wallet card		X									
IBDQ		X						X			X
WPAI		X						X			X
IBD-DI		X						X			X
Health outcomes, CD-related events			X		X		X	X		X	X
Patient diary	X	X	X	X	X	X	X	X	X	X	X

Induction Phase (Screening Through Week 26)											
	Screening	Treatment									
Study Week		Wk 0	Wk 2	Wk 4 (r)	Wk 6	Wk 8 (r)	Wk 10	Wk 14	Wk 18 (r)	Wk 22	Wk 26
Study Day ± Visit Window (Days)	Day -28 to Day -1	1	15 ±3	n/a	43 ±3	n/a	71 ±3	99 ±3	n/a	155 ±7	183 ±7
Visit Number:	1	2	3	n/a	4	n/a	5	6	n/a	7	8
C difficile test (q)											
CD Risk by clinical assessment, PROSPECT Tool or 2014 AGA CD Care Pathway	X										
Monitr CD Test		X									X

Footnotes are on last table page.

Maintenance Phase (Week 30 Through Week 128)															
	Treatment														
Study Week	**Wk 30**	**Wk 34 (s)**	**Wk 38**	**Wk 42 (s)**	**Wk 46**	**Wk 50 (s)**	**Wk 52**	**Wk 54**	**Wk 58 (s)**	**Wk 62**	**Wk 66 (s)**	**Wk 70**	**Wk 74 (s)**	**Wk 78**	**Wk 82 (s)**
Study Day ± Visit Window (Days)	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**365 ±7**	**379 ±3**	**407 ±7**	**435 ±7**	**463 ±7**	**491 ±7**	**519 ±7**	**547 ±7**	**575 ±7**
Visit Number:	**9**	**9b**	**10**	**10b**	**11**	**11b**	**12**	**13**	**13b**	**14**	**14b**	**15**	**15b**	**16**	**16b**
Physical examination	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
Vital signs (a)	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
Access IRT to register visit	X	X (s)	X	X (s)	X	X (s)		X	X (s)	X	X (s)	X	X (s)	X	X (s)
CDAI	X		X		X		X	X		X		X		X	
PRO-2							X							X	
Ileocolonoscopy (b)															
SES-CD															
CRP							X							X	
Fecal calprotectin (c)							X							X	
Chemistry, Hematology, Urinalysis	X (e)		X		X		X	X		X		X		X	
PK samples for vedolizumab (g)			X					X				X			
ADAs samples, vedolizumab			X					X				X			
ADAs samples, adalimumab			X					X				X			
Pregnancy test (hCG) (i)	X														
Urine pregnancy test (i)	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Home pregnancy test (j)		X		X		X			X						
Vedolizumab (IV) (k)	X	X (s)	X	X (s)	X	X (s)		X	X (s)	X	X (s)	X	X (s)	X	X (s)
Methotrexate (PO) (n)	X	X													
Folic acid (PO) (o)	X	X													

Maintenance Phase (Week 30 Through Week 128)															
	Treatment														
Study Week	**Wk 30**	**Wk 34 (s)**	**Wk 38**	**Wk 42 (s)**	**Wk 46**	**Wk 50 (s)**	**Wk 52**	**Wk 54**	**Wk 58 (s)**	**Wk 62**	**Wk 66 (s)**	**Wk 70**	**Wk 74 (s)**	**Wk 78**	**Wk 82 (s)**
Study Day ± Visit Window (Days)	**211 ±7**	**239 ±7**	**267 ±7**	**295 ±7**	**323 ±7**	**351 ±7**	**365 ±7**	**379 ±3**	**407 ±7**	**435 ±7**	**463 ±7**	**491 ±7**	**519 ±7**	**547 ±7**	**575 ±7**
Visit Number:	**9**	**9b**	**10**	**10b**	**11**	**11b**	**12**	**13**	**13b**	**14**	**14b**	**15**	**15b**	**16**	**16b**
AE/SAE assessment	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
Concomitant medications/procedures	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
PML checklist (p)	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
PML wallet card															
IBDQ							X							X	
WPAI							X							X	
IBD-DI							X							X	
Health outcomes, CD-related events	X		X		X		X	X		X		X		X	
Patient diary	X	X (s)	X	X (s)	X	X (s)	X	X	X (s)	X	X (s)	X	X (s)	X	X (s)
LTFU questionnaire															
***C difficile* test (q)**															

Footnotes are on last table page.

Maintenance Phase (Week 30 Through Week 128) (continued)							
	Treatment					EOS or ET	LTFU Phone Call
Study Week	Wk 86	Wk 90 (s)	Wk 94	Wk 98 (s)	Wk 102 EOT	Wk 120 (18 wks post tx)	Wk 128 (26 wks post tx)
Study Day ± Visit Window (Days)	603 ±7	631 ±7	659 ±7	687 ±7	715 ±7	841 ±7	897 ±7
Visit Number:	17	17b	18	18b	19	20	21
Physical examination	X	X (s)	X	X (s)	X	X	
Vital signs (a)	X	X (s)	X	X (s)	X	X	
Access IRT to register visit	X	X (s)	X	X (s)	X	X	
CDAI	X		X		X	X	
PRO-2					X		
Ileocolonoscopy (b)					X	X (ET only)	
SES-CD					X		
CRP					X		
Fecal calprotectin (c)					X		
Chemistry, Hematology, Urinalysis	X		X		X	X	
PK samples for vedolizumab (g)	X				X		
ADAs samples, vedolizumab	X				X		
ADAs samples, adalimumab	X				X		
Pregnancy test (hCG) (i)						(X)	
Urine pregnancy test (i)	X	X	X	X	X	X	
Home pregnancy test (j)							
Vedolizumab (IV) (k)	X	X (s)	X	X (s)	X		
Methotrexate (PO) (n)							
Folic acid (PO) (o)							
AE/SAE assessment	X	X (s)	X	X (s)	X	X	
Concomitant medications/procedures	X	X (s)	X	X (s)	X	X	
PML checklist (p)	X	X (s)	X	X (s)	X		
PML wallet card					X		

Maintenance Phase (Week 30 Through Week 128) (continued)							
	Treatment					**EOS or ET**	**LTFU Phone Call**
Study Week	**Wk 86**	**Wk 90 (s)**	**Wk 94**	**Wk 98 (s)**	**Wk 102 EOT**	**Wk 120 (18 wks post tx)**	**Wk 128 (26 wks post tx)**
Study Day ± Visit Window (Days)	**603 ±7**	**631 ±7**	**659 ±7**	**687 ±7**	**715 ±7**	**841 ±7**	**897 ±7**
Visit Number:	**17**	**17b**	**18**	**18b**	**19**	**20**	**21**
IBDQ					X		
WPAI					X		
IBD-DI					X		
Health outcomes, CD-related events	X		X		X	X	
Patient diary	X	X (s)	X	X (s)	X	X	
LTFU questionnaire							X
***C difficile* test (q)**							
Monitr CD Test					X	X (ET only)	

Abbreviations; AE, adverse event; ADA, antidrug antibodies; ANCA, perinuclear antineutrophil antibody; ASCA, anti-*Saccharomyces cerevisiae* antibody; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, early termination; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IBD-DI, Inflammatory Bowel Disease Disability Index; IBDQ, Inflammatory Bowel Disease Questionnaire; ID, identification; IgA, immunoglobin; IRT, interactive response technology; IV, intravenous; LTFU, long-term follow-up; n/a=not applicable; NOD2, nucleotide-binding oligomerization domain-containing protein 2; PK, pharmacokinetic; PML, progressive multifocal leukoencephalopathy; PO, oral; PRO-2, patient-reported outcome 2; RNA, ribonucleic acid; SAE, serious adverse event; SC, subcutaneous; SES-CD, simple endoscopic score for Crohn's disease; tx, treatment; WPAI,Work Productivity and Activity Impairment; hsCRP, high-sensitivity C-reactive protein; SAA 1, serum amyloid A 1; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1: VCAM 1, vascular cell adhesion molecule 1; IL 7, interleukin-7; TGFα, transforming growth factor α; EMMPRIN, extracellular matrix metalloproteinase inducer; MMP, matrix metalloproteinase.

(a) Height collected only at the screening visit. Weight will be measured at every site visit where CDAI is calculated.

(b) Endoscopy to be collected at screening, Weeks 26 and 102, or early termination for central read. Biopsies will also be collected. All biopsies collected per protocol will be centrally stored and analyzed at the end of the study. Although it is permissible for the investigator to take additional biopsy samples as deemed necessary for standard of care management of the patient during the protocol required colonoscopy, these will be considered as occurring outside the protocol. Such collection, handling, and analyses of the additional samples will be and remain the responsibility of the investigator.

(c) Stool sample to be collected from the first bowel movement in the morning and sent to central laboratory.

(d) QuantiFERON test or tuberculin skin test only.

(e) Hematology only.

(f) DNA and RNA samples will be collected on Day 1.

(g) PK samples for vedolizumab to be collected predose on dosing days Day 1 and Weeks 6, 10, 14, 26, 38, 54, 70, 86, and 102. at visits where study drug is given.

(h) PK samples for adalimumab to be collected predose on dosing days (prior to vedolizumab dosing) on Day 1 and Weeks 6, 10, 14, 22, and 26. For Weeks 6, 14, and 22, when the subject is self-administering adalimumab at home, the adalimumab PK samples will be collected on the day of vedolizumab PK collection, prior to vedolizumab infusion.

(i) 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 or Early Termination if stopped prior to Week 30; urine pregnancy to be completed at other visits.

(j) Women of childbearing potential only. When site visits shift from every 4 weeks to every 8 weeks, women of childbearing potential will need to take a home pregnancy test every other month (in between visits) up until Week 58 and report the results to the site. If the subject experiences an exacerbation and switches to Q4W dosing, then no home pregnancy test is required as subject will have urine pregnancy test performed on site before infusion.

(k) Vedolizumab IV 300 mg at Week 0, 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, and 102. Subjects should be observed for 2 hours following the first 2 infusions, at a minimum, and 1 hour after each subsequent infusion for monitoring hypersensitivity reactions.

(l) Adalimumab SC 160 mg at Week 0, 80 mg at Week 2, then 40 mg every 2 weeks for a total of 27 weeks. Self injection or caregiver may inject using either the Pen or prefilled syringe if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique. Adalimumab will be self-administered at home at Weeks 2, 4, 8, 10, 12, 16, 18, 20, 24, and 26.

(m) At Weeks 0, 2, 6, 14, and 22, adalimumab will be administered 1 day after the vedolizumab infusion. For Week 0, the subject should return to the site the day after (or within a 3-day window of) the vedolizumab infusion to self-administer the adalimumab SC injection while instructed and observed by site staff or to have the injection administered by qualified site staff. Subsequent doses will be self-administered at home starting at Week 2.

(n) Methotrexate 15 mg (six 2.5-mg tablets) PO once weekly for total of 34 weeks.

(o) Daily folic acid (1 mg PO capsule or tablet) must be taken during the 34-week period of methotrexate treatment.

(p) PML checklist must be administered at screening and prior to vedolizumab dosing at every vedolizumab dosing visit.

(q) A *C difficile* test will be done only if a subject experiences a flare up during the study.

(r) Not a clinic visit. Home dosing with adalimumab and methotrexate only.

(s) Optional 4-week vedolizumab dosing visit. If a subject has a first exacerbation of CD after 26 weeks (defined as a CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval, OR objective evidence of disease activity by colonoscopy and CRP above normal, OR fecal calprotectin >250 µg/g alone), then frequency of vedolizumab infusions will be changed to vedolizumab 300 mg IV every 4 weeks (instead of every 8 weeks) for the remainder of treatment. Subjects should be monitored for 1 hour after each infusion for hypersensitivity reactions.

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 (nonroutine/nonstandard 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 medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

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

Appendix D Investigator Consent to Use of Personal Information

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

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

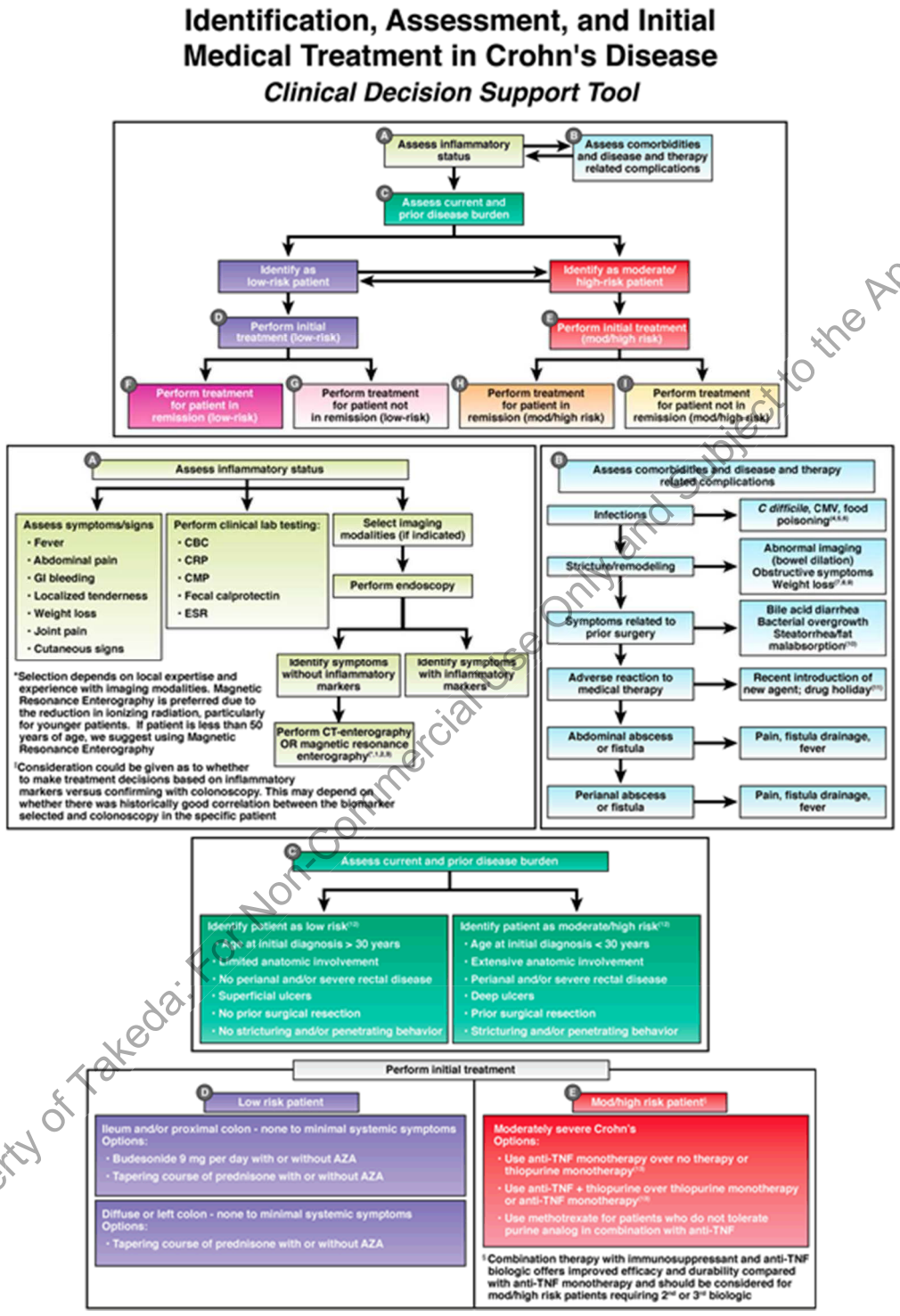
Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

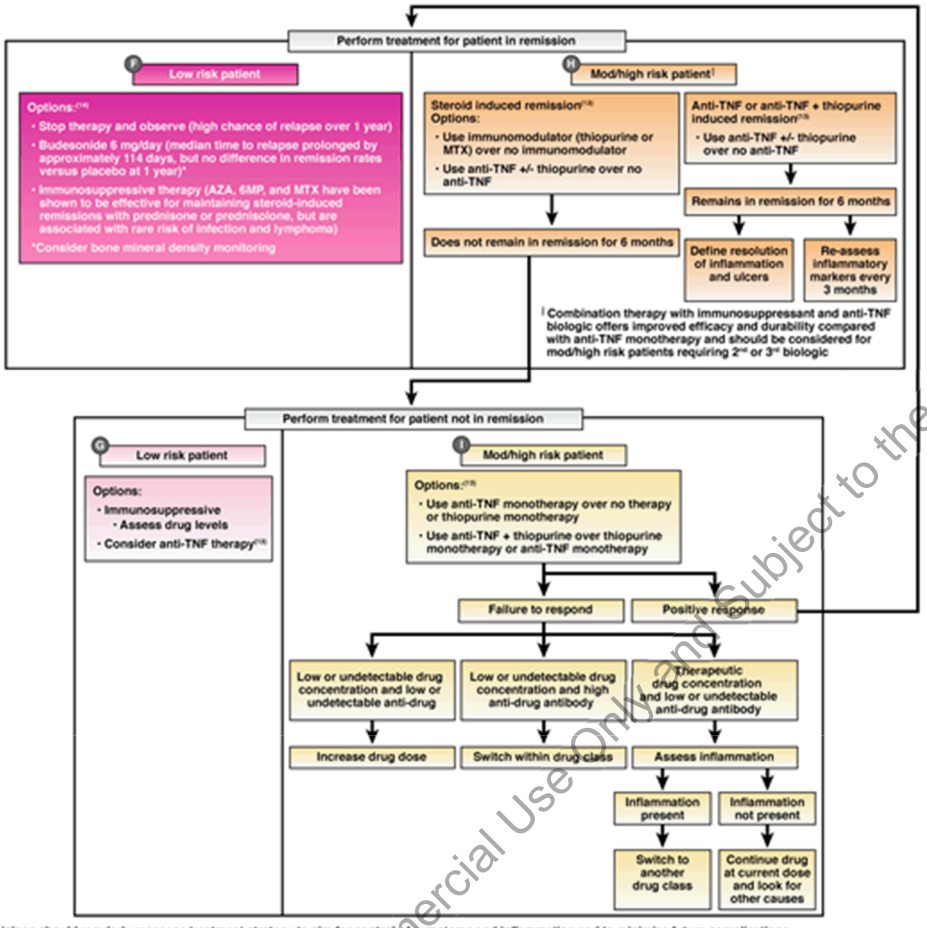
- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission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

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

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

Appendix E AGA CD Clinical Care Pathway





Clinicians should regularly reassess treatment strategy to aim for control of symptoms and inflammation and to minimize future complications

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Source: Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. Gastroenterology. 2014:147:702-705.

Appendix F SES-CD

	SES-CD values			
Variable	**0**	**1**	**2**	**3**
Ulcers	None	Aphthous ulcers (Diameter 0.1-0.5 cm)	Large ulcers (Diameter 0.5-2 cm)	Very large ulcers (Diameter >2 cm)
Ulcerated surface	None	<10%	10% - 30%	>30%
Affected surface	Unaffected segment	<50%	50% - 75%	>75%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Source: Adapted from: Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004; 60:505-12.

Abbreviation: SES-CD, Simple Endocopic Score for Crohn's Disease.

Appendix G 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.

Abbreviation: CDAI, Crohn's Disease Acivity Index,

(a) If hematocrit subtotal <0, enter 0. (b) If body weight subtotal <-10, enter -10.

Appendix H 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 I PRO-2

Variable	Count	7-day Average	Multiplication Factor	Total
Number of liquid or very soft stools	7-day average number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		x 2	
Abdominal pain	7-day average 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	
PRO-2 SCORE			Add totals:	

Source: Adapted from: Khanna R, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther. 2015 Jan;41(1):77-86.
Abbreviation: PRO-2, patient-reported outcome 2.

Appendix J IBDQ

The 32-item McMaster University IBDQ will be employed to assess for changes in quality of life in each subject at select study visits relative to Baseline, based on bowel function, systemic symptoms, social function and emotional state. This questionnaire will be completed by each subject prior to any clinical assessment and will be based on a 2-week recall period.

Instructions for the 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. On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and answer 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?

Please choose only 1 number:

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 has it been affected by your bowel problem? Then answer the question as best as you can. You will have a chance to ask the nurse questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

(IBDQ)

1. How frequent have your bowel movements been during the last 2 weeks? Please indicate how frequent your bowel movements have been during the last 2 weeks by picking 1 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 past 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 1 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.

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 over 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.

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 the washroom (bathroom, toilet)? 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.

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.

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom (bathroom, toilet) 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 and option from:

1. A major problem.
2. A big problem.
3. A significant problem.
4. Some trouble.
5. A little trouble.
6. Hardly any of the time.
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 of the time.
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.

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 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.

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.

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 last 2 weeks have you felt a lack of understanding from others? Please choose 1 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.

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose 1 of the following options from:

1. Very dissatisfied, unhappy most of the time
2. General 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 K Collection, Storage, and Shipment of Bioanalytical Samples

Vedolizumab

Instructions for Processing of Serum Samples for PK Vedolizumab Analysis

1. Collect 5 mL of venous blood into a Becton-Dickinson Vacutainer. For all vedolizumab samples, blood samples should be collected into glass red stopper vacutainers. Direct venipuncture is the only method of blood collection.
2. Allow the glass red top Vacutainer to sit at room temperature for approximately 60 minutes (refer to product information for correct time) to ensure proper clot formation.
3. To separate the serum samples, centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 relative centrifugal force (RCF) at room temperature in a centrifuge. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. To ensure a more homogeneous sample, all serum should first be transferred into 1 aliquot. From there, mix well and split the serum evenly between the 2 aliquots into polypropylene tubes. A minimum of 0.8 mL needs to be obtained for each sample.
5. Cap the labeled storage tubes and freeze the serum samples immediately at approximately -20°C. No more than 1 hour and 45 minutes must be allowed to elapse between collecting blood and freezing the serum sample.
6. Keep samples frozen at approximately -20°C or lower until shipment to PPD Central Lab, Highland Heights, KY. "SET 1" samples will be shipped first on dry ice, followed by shipment of duplicate "SET 2" samples after "SET 1" samples have been received.

Shipping of Serum Samples for PK Analysis for Vedolizumab

The investigative site will ship samples to PPD Central Laboratory on a monthly basis using the laboratory carton (kit) provided, following packaging and shipping instructions provided in the central laboratory manual.

Adalimumab

Instructions for Processing of Serum Samples for PK Adalimumab Analysis

1. Collect 5 mL of venous blood into a Becton-Dickinson Vacutainer. For all adalimumab samples, blood samples should be collected into glass red stopper vacutainers. Direct venipuncture is the only method of blood collection.
2. Allow the glass red top Vacutainer to sit at room temperature for approximately 60 minutes (refer to product information for correct time) to ensure proper clot formation.
3. To separate the serum samples, centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 RCF at room temperature in a centrifuge. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.

4. To ensure a more homogeneous sample, all serum should first be transferred into 1 aliquot. From there, mix well and split the serum evenly between the 2 aliquots into polypropylene tubes. A minimum of 0.8 mL needs to be obtained for each sample.
5. Cap the labeled storage tubes and freeze the serum samples immediately at approximately -70°C. No more than 1 hour and 45 minutes must be allowed to elapse between collecting blood and freezing the serum sample.
6. Keep samples frozen at approximately -70°C or lower until shipment to PPD Central Lab, Highland Heights, KY. "SET 1" samples will be shipped first on dry ice, followed by shipment of duplicate "SET 2" samples after "SET 1" samples have been received.

Shipping of Serum Samples for PK Analysis for Adalimumab

The investigative site will ship samples to PPD Central Laboratory on a monthly basis using the laboratory carton (kit) provided, following packaging and shipping instructions provided in the central laboratory manual.

Appendix L Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 04. Minor editorial changes that had no impact on content have not been detailed here.

Change 1: Takeda address was updated.

Initial wording:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015
Amended or new wording:	Takeda Development Center Americas, Inc. ~~One Takeda Parkway~~ 95 Hayden Avenue ~~Deerfield, IL 60015~~ Lexington, MA 02421

Rationale for Change: Corporate address change.

Change 2: Section 1.1 Robarts Medical Monitor phone was updated.

The primary change occurs in Section 1.1 Contacts.

Initial wording:	PPD
Amended or new wording:	PPD

Rationale for Change: Change in personnel.

Change 3: Section 1.1 Responsible Medical Officer contact was updated.

The primary change occurs in Section 1.1 Contacts.

Initial wording:	PPD
Amended or new wording:	PPD

Rationale for Change: Change in personnel.

Change 4: Sections 2.0 and 6.1 were updated to increase site number from 60-64.

The primary change occurs in Section 2.0 STUDY SUMMARY.

Initial wording:	Approximately 60 sites in the United States and Canada
Amended or new wording:	Approximately ~~60~~ 64 sites in the United States and Canada

Rationale for Change: To add additional sites to contribute to enrollment.

Section 6.1 Study Design also contains this change.

Change 5: Section 4.1.2.2 was updated with the latest exposure data from Investigator Brochure Edition 23 dated 12 July 2019.

The primary change occurs in Section 4.1.2.2 Human Experience.

Initial wording:	As of 19 May 2015, approximately 3600 subjects (309 healthy subjects, 1393 subjects with UC, and 1896 subjects with CD) have received at least 1 dose of vedolizumab across all studies in the clinical development program (see current version of Investigator's Brochure). Vedolizumab exposure has extended for ≥12 months in 1667 subjects, ≥24 months in 1306 subjects, ≥36 months in 935 subjects, ≥48 months in 676 subjects, ≥60 months in 267 subjects, and ≥72 months in 26 subjects as of 19 May 2015. Based on drug shipment data, the patient exposure to vedolizumab since its approval in May 2014 is estimated to be approximately 11,943 patient-years.
Amended or new wording:	As of 19 May ~~2015~~ 2019, approximately ~~3600~~ 6376 subjects (~~309~~ 679 healthy subjects, ~~1393~~ 2671 subjects with UC, and ~~1896~~ 2920 subjects with CD) have received at least 1 dose of vedolizumab across all studies in the clinical development program (see current version of Investigator's Brochure). Vedolizumab exposure has extended for ≥12 months in ~~1667~~ 2553 subjects, ≥24 months in ~~1306~~ 1636 subjects, ≥36 months in ~~935~~ 1126 subjects, ≥48 months in ~~676~~ 908 subjects, ≥60 months in ~~267~~ 675 subjects, and ≥72 months in ~~26~~ 378 subjects as of 19 May ~~2015~~ 2019. Based on drug shipment data, the patient exposure to vedolizumab since its approval in May 2014 is estimated to be approximately ~~11,943~~ 336,400 patient-years.

Rationale for Change: Updated with the latest exposure data from Investigator Brochure Edition 23 dated 12 July 2019.

Change 6: Section 5.1.3 was updated to include the additional objective for Monitr CD testing.

The primary change occurs in Section 5.1.3 Additional Objectives.

New wording:
- To evaluate endoscopic remission, defined as Monitr CD Endoscopic Healing Index (EHI) score ≤20, at Weeks 26 and 102.
- To evaluate Monitr CD EHI score ≤30 or ≤50 at Weeks 26 and 102.

Rationale for Change: The primary endpoint of the study is Week 26 endoscopic remission which requires patients to go through a Week 26 endoscopy. Another endoscopy is required at Week 102 to evaluate the secondary endpoint of maintenance of remission. As a result of COVID-19 situation and to ensure safety of patients and hospital staff, endoscopies are not being performed at many sites. In order to ensure the safety of the subjects and to be able to still capture some relevant data on mucosal healing at Week 26 and Week 102 we are introducing the Monitr CD tool.

Change 7: Section 5.2.3 was updated to include endpoints for Monitr CD testing.

The primary change occurs in Section 5.2.3 Additional Endpoints.

New wording:
- Percentage of subjects with an EHI score ≤20 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤30 at Weeks 26 and 102.
- Percentage of subjects with an EHI score ≤50 at Weeks 26 and 102.
- Change from baseline in EHI score at Weeks 26 and 102.

Rationale for Change: The primary endpoint of the study is Week 26 endoscopic remission which requires patients to go through a Week 26 endoscopy. Another endoscopy is required at Week 102 to evaluate the secondary endpoint of maintenance of remission. As a result of COVID-19 situation and to ensure safety of patients and hospital staff, endoscopies are not being performed at many sites. In order to ensure the safety of the subjects and to be able to still capture some relevant data on mucosal healing at Week 26 and Week 102 we are introducing the Monitr CD tool.

Change 8: Sections 7.3.1.2, 8.1.3, 9.3.6, and Appendix A footnote (s) were updated to clarify exacerbation of CD language.

The primary change occurs in Section 7.3.1.2 Medications for CD Exacerbation After 26 Weeks.

Initial wording:
- A CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week interval and objective evidence of disease activity by colonoscopy and CRP above normal, OR
- Fecal calprotectin >250 µg/g alone.

Amended or new
- A CDAI increase of >70 from the prior visit on 2 occasions separated by a 2-week

wording: interval, OR

- Objective evidence of disease activity by colonoscopy and CRP above normal, OR
- Fecal calprotectin >250 µg/g alone.

Rationale for Change: Clarification of existing text.

Section 8.1.3 Dose and Regimen, and Section 9.3.6 Unscheduled Visits Due to Exacerbation of CD and Appendix A Schedule of Study Procedures also contain this change.

Change 9: Section 7.4 Adverse Event withdrawal criteria was clarified to include criteria for Leukopenia or Lymphopenia.

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

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

- LFT Abnormalities

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

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

- LFT Abnormalities

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

- Leukopenia or Lymphopenia. WBC and lymphocyte counts will be monitored for all subjects. Methotrexate, if applicable, should be discontinued and the dose of study drug held for an absolute lymphocyte count <0.5 × 109/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of study drug can be administered only if the absolute lymphocyte count is ≥0.5 × 109/L. If the absolute lymphocyte count remains <0.5 × 109/L, study drug should be discontinued and the subject withdrawn from the study.

Rationale for Change: Patients with severe leukopenia/lymphopenia are at increased risk of developing infections; opportunistic and infections for which gut is a defensive barrier are potential risks for vedolizumab.

Change 10: Section 9.1.4 genitourinary system was removed from physical exam procedures.

The primary change occurs in Section 9.1.4 Physical Examination Procedure.

Initial wording:	A 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; (11) genitourinary system; and (12) 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.
Amended or new wording:	A 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; ~~(11) genitourinary system;~~ and (~~12~~ 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.

Rationale for Change: Clarification of existing text.

Change 11: Section 9.1.10 and Appendix A Schedule of Procedures table updated to include Monitr CD testing.

The primary change occurs in Section 9.1.10.4 Monitr Crohn's Disease Test.

New wording:	The Monitr Crohn's Disease Test is a laboratory-developed test from Prometheus Labs that evaluates multiple markers of mucosal damage and repair processes, regardless of disease location. It applies a proprietary algorithm to 13 biomarkers to produce a quantitative Endoscopic Healing Index Score, ranging from 0 to 100, to aid in distinguishing endoscopic remission from active disease in adult CD patients. A blood sample for Monitr CD will be collected at Week 26 and Week 102 or early termination. In addition, Baseline Week 0, Week 26 and Week 102 samples may be analyzed for subjects who have already completed those visits prior to Amendment #4. After PK and Immunogenicity testing are completed, any residual frozen serum aliquots from PK and/or Immunogenicity testing may be repurposed for this testing. These samples will only be used after receiving subject consent/reconsent. Further instruction on the collection and handling of these samples can be found in the study Laboratory Manual.

Rationale for Change: The primary endpoint of the study is Week 26 endoscopic remission which requires patients to go through a Week 26 endoscopy. Another endoscopy is required at Week 102 to evaluate the secondary endpoint of maintenance of remission. As a result of COVID-19 situation and to ensure safety of patients and hospital staff, endoscopies are not being performed at many sites. In order to ensure the safety of the subjects and to be able to still capture some relevant data on mucosal healing at Week 26 and Week 102 we are introducing the Monitr CD tool.

Appendix A Schedule of Study Procedures also contains this change.

Change 12: Section 9.1.11 and Appendix A Schedule of Procedures table and footnote (b) clarified colonoscopy may be performed at Early Termination visit.

The primary change occurs in Section 9.1.11 Colonoscopy and Biopsy Procedure.

Initial wording:	Colonoscopy will be performed during screening and at Weeks 26 and 102. All study colonoscopies will be video-recorded using the Robarts Central Image Management Solution (CIMS). All study endoscopy videos will be subject to central review to ensure consistent grading. A central reviewer will confirm the SES-CD inclusion criterion prior to subject enrollment. Central reviewer's grading will stand as final assessment for eligibility. CIMS will communicate incidental findings observed during central review to the investigator/study team for additional follow up.
Amended or new	Colonoscopy will be performed during screening and at Weeks 26 and 102 or early termination. All study colonoscopies will be video-recorded using the Robarts Central

wording:	Image Management Solution (CIMS). All study endoscopy videos will be subject to central review to ensure consistent grading. A central reviewer will confirm the SES-CD inclusion criterion prior to subject enrollment. Central reviewer's grading will stand as final assessment for eligibility. CIMS will communicate incidental findings observed during central review to the investigator/study team for additional follow up.

Rationale for Change: To allow for colonoscopy collection at early termination.

Appendix A Schedule of Study Procedures also contain this change.

Change 13: Section 9.1.20 approximate total blood volume was updated.

The primary change occurs in Section 9.1.20 Procedures for Clinical Laboratory Samples.

Initial wording:	All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 45.2 mL, and the approximate total volume of blood for the study is 464.2 mL. Details of these procedures, specimen handling and required safety monitoring will be given in the laboratory manual.
Amended or new wording:	All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately ~~45.2~~ 45 mL, and the approximate total volume of blood for the study is ~~464.2~~ 476 mL. Details of these procedures, specimen handling and required safety monitoring will be given in the laboratory manual.

Rationale for Change: Blood volume updated to include Monitr CD testing.

Change 14: Table 9.a was updated to include Monitr CD biomarkers.

The primary change occurs in Table 9.a Clinical Laboratory Tests.

New wording:	Monitr CD Test (biomarker panel using serum to measure hsCRP, SAA 1, CEACAM 1, VCAM 1, ANG 1, ANG 2, IL-7, TGFα, EMMPRIN, MMP 1, MMP 2, MMP 3, and MMP 9) hsCRP, high-sensitivity C-reactive protein; SAA 1, serum amyloid A 1; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1: VCAM 1, vascular cell adhesion molecule 1; IL-7, interleukin-7; TGFα, transforming growth factor α; EMMPRIN, extracellular matrix metalloproteinase inducer; MMP, matrix metalloproteinase

Rationale for Change: The primary endpoint of the study is Week 26 endoscopic remission which requires patients to go through a Week 26 endoscopy. Another endoscopy is required at Week 102 to evaluate the secondary endpoint of maintenance of remission. As a result of COVID-19 situation and to ensure safety of patients and hospital staff, endoscopies are not being performed at many sites. In order to ensure the safety of the subjects and to be able to still capture some relevant data on mucosal healing at Week 26 and Week 102 we are introducing the Monitr CD tool.

Appendix A Schedule of Study Procedures also contains this change.

Change 15: Section 9.1.24 clarification of predose ADA sample collection timing.

The primary change occurs in Section 9.1.24 Anti-Drug Antibodies Sampling.

Initial wording:	Blood samples for ADA assessments for vedolizumab will be obtained on Day 1 and within 30 minutes prior to dosing at the time points indicated in the Schedule of Study Procedures (Appendix A). Blood samples for ADA assessments for adalimumab will be obtained on Day 1 and within 30 minutes prior to vedolizumab dosing at the time points indicated in the Schedule of Study Procedures (Appendix A).
Amended or new wording:	Blood samples for ADA assessments for vedolizumab will be obtained on Day 1 ~~and within 30 minutes~~ prior to dosing at the time points indicated in the Schedule of Study Procedures (Appendix A). Blood samples for ADA assessments for adalimumab will be obtained on Day 1 ~~and within 30 minutes~~ prior to vedolizumab dosing at the time points indicated in the Schedule of Study Procedures (Appendix A).

Rationale for Change: Clarification of existing text.

Change 16: Section 9.1.27.3 correction of reason for use of barrier methods (b).

The primary change occurs in Section 9.1.27.3 Definitions and Procedures for Contraception and Pregnancy Avoidance.

Initial wording:	b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
Amended or new wording:	b) Reasons for use of barrier methods (ie, condom) in males with ~~pregnant~~ female partners of childbearing potential.

Rationale for Change: Clarification of existing text.

Change 17: Appendix A Schedule of Procedures table and footnote (j) were updated to clarify pregnancy testing for Q4 dosing.

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

Initial wording:	(j) Women of childbearing potential only. When site visits shift from every 4 weeks to every 8 weeks, women of childbearing potential will need to take a home pregnancy test every other month (in between visits) up until Week 58 and report the results to the site.
Amended or new wording:	(j) Women of childbearing potential only. When site visits shift from every 4 weeks to every 8 weeks, women of childbearing potential will need to take a home pregnancy test every other month (in between visits) up until Week 58 and report the results to the site. If the subject experiences an exacerbation and switches to Q4W dosing, then no home pregnancy test is required as subject will have urine pregnancy test performed on site before infusion.

Rationale for Change: Clarification of existing text.

Change 18: Appendix A Schedule of Procedures footnote (a) was updated to clarify weight measurement visits.

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

Initial wording:	(a) Height collected only at the screening visit.
Amended or new wording:	(a) Height collected only at the screening visit. Weight will be measured at every site visit where CDAI is calculated.

Rationale for Change: Clarification of existing text.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Medical Affairs Approval	01-Jul-2020 21:42 UTC
	Biostatistics Approval	02-Jul-2020 15:38 UTC