Title: A Phase 2, Randomized, Double-Blind, Dose-Ranging Study to Determine the Pharmacokinetics, Safety and Tolerability of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

NCT Number: NCT03138655

Protocol Approve Date: 30 August 2019

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

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

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

PROTOCOL AMENDMENT

A Phase 2, Randomized, Double-Blind, Dose-Ranging Study to Determine the Pharmacokinetics, Safety and Tolerability of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

A Phase 2, Randomized, Double-Blind, Dose-Ranging Study With Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway, Deerfield, IL 60015, USA Takeda Development Centre Europe, Ltd. 61 Aldwych, London, WC2B 4AE, United Kingdom		
Study Number:	MLN0002-2003		
IND Number:	009125	**EudraCT Number:**	2017-002231-41
Compound:	Vedolizumab IV		
Date:	30 August 2019	**Amendment Number:**	04

Amendment History

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
07 October 2016	Initial	NA	Global
07 April 2017	01	Substantial	Global
30 May 2017	02	Nonsubstantial	Global
17 January 2018	03	Substantial	Global
30 August 2019	04	Nonsubstantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

Contact Type/Role	Americas and Europe TDC Contact
Serious adverse event and pregnancy reporting	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 (and other signatories, as applicable) can be found on the signature page.

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

PPD

INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 04 Summary of Changes

Rationale for Amendment 04

This document describes the changes in reference to the Protocol Incorporating Amendment No. 04. The primary purpose of this amendment is to clarify procedures for completion and review of entries to diaries, and to define the minimum number of completed subjects in either weight group before interim analysis is undertaken.

Study personnel and corresponding contact details have been updated. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes, the rationale for the changes, and where the changes are located, see Appendix J.

Changes in Amendment 04

1. Clarified procedures for completion and review of entries to diaries.
2. Clarification of criteria for interim analysis.
3. Amended the concomitant oral corticosteroid dosing information.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc. Takeda Development Centre Europe, Ltd.	**Compound:** Vedolizumab IV	
Title of Protocol: A Phase 2, Randomized, Double-Blind, Dose-Ranging Study to Determine the Pharmacokinetics, Safety, and Tolerability of Vedolizumab IV in Pediatric Subjects With Ulcerative Colitis or Crohn's Disease	**IND No.:** 009125	**EudraCT No.:** 2017-002231-41
Study Number: MLN0002-2003	**Phase:** 2	

Study Design:

This is a phase 2, randomized, double-blind, dose-ranging study enrolling male and female pediatric subjects (2 to 17 years, inclusive) who weigh ≥10 kg with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD) and who have demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents: corticosteroids, immunomodulators, and/or tumor necrosis factor-alpha (TNF-α) antagonist therapy. The study will evaluate the pharmacokinetics (PK), efficacy, immunogenicity, safety, and tolerability of vedolizumab IV administered by intravenous (IV) infusion. Approximately 80 pediatric subjects will be enrolled to ensure that 40 subjects weighing ≥30 kg and 40 subjects weighing 10 kg to <30 kg, as well as a minimum of 36 subjects with UC and a minimum of 36 subjects with CD, will be enrolled in the study.

Eligible subjects will receive vedolizumab infusions at Day 1 and Weeks 2, 6, and 14. The study will allow characterization of Week 14 PK and efficacy and the study will continue to Week 22. After completing the Week 22 Visit procedures, eligible subjects may enter an extension study. Those subjects who do not enter the extension study will have a Final Safety Visit 18 weeks after their last dose of study drug and participate in a long-term follow-up safety survey by telephone 6 months after their last dose of study drug.

Primary Objective:

To evaluate vedolizumab PK in pediatric subjects with UC or CD.

Secondary Objectives:

- To assess the efficacy of vedolizumab IV in pediatric subjects with UC or CD.
- To characterize the dose-response relationship of vedolizumab IV in pediatric subjects with UC or CD.

Subject Population: Male and female pediatric subjects 2 to 17 years, inclusive, who weigh ≥10 kg and who have moderately to severely active UC or CD.

Number of Subjects: Approximately 80 subjects (subjects who discontinue may be replaced as determined by the sponsor).	**Number of Sites:** Estimated total: 72 sites in North America, Europe, and Middle East.
Dose Level(s) (at Study Entry): Subjects weighing ≥30 kg before the first dose in the study will be randomly assigned to receive 300 mg (high dose) or 150 mg (low dose) vedolizumab IV. Subjects weighing <30 kg before the first dose in the study will be randomly assigned to receive 200 mg (high dose) or 100 mg (low dose) vedolizumab IV.	**Route of Administration:** IV

Duration of Treatment:	**Period of Evaluation:**
22 weeks	This phase 2 study includes a 4-week Screening Period, a 22-week Treatment Period (with last dose at Week 14). Subjects who do not enter the extension study will have an 18-week Follow-up Period starting from their last dose of study drug and a long-term follow-up safety survey by telephone 6 months after their last dose of study drug.

Main Criteria for Inclusion:

- The subject:
  a) is male or female; and
  b) weighs ≥10 kg at the time of randomization; and
  c) is 2 to 17 years, inclusive, at the time of randomization, with moderately to severely active UC or CD diagnosed at least 3 months prior to Screening by clinical and endoscopic evidence and corroborated by a histopathology report.
- The subject has demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents: corticosteroids, immunomodulators, and/or TNF-α antagonist therapy.
- The subject has a medical history of moderately to severely active UC during Screening defined as a complete Mayo score of 6 to 12, and a total of Mayo subscores of stool frequency and rectal bleeding ≥4 and an endoscopy subscore ≥2; or has moderately to severely active CD defined as simple endoscopic score for Crohn's disease (SES-CD) ≥7, and the Crohn's Disease Activity Index (CDAI) components of average daily Abdominal Pain Score of >1 for the 7 days prior, and total number of liquid/very soft stools >10 for the 7 days prior to the first dose of study drug.
- The subject has evidence of UC extending proximal to the rectum (ie, not limited to proctitis) or evidence of CD involving the ileum and/or colon, at a minimum.
- Subjects with extensive colitis or pancolitis of >8 years duration or left-sided colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months prior to their first dose of study drug.

Main Criteria for Exclusion:

- The subject has had previous exposure to approved or investigational anti-integrins including, but not limited to, natalizumab, efalizumab, etrolizumab, or AMG 181, or mucosal addressin cell adhesion molecule-1 (MAdCAM-1) antagonists, or rituximab.
- The subject has had prior exposure to vedolizumab.
- The subject has had hypersensitivity or allergies to any of the vedolizumab excipients.
- The subject has received:
  a) any investigational biologic (other than those listed in Exclusion Criterion #1) within 60 days or 5 half-lives prior to Screening (whichever is longer).
  b) an approved biologic or biosimilar agent within 2 weeks prior to the first dose of the study drug or at any time during the Screening period.
- The subject has a positive progressive multifocal leukoencephalopathy (PML) subjective symptom checklist prior to the administration of the first dose of study drug.
- The subject currently requires surgical intervention for UC or CD, or is anticipated to require surgical intervention for UC or CD during this study.
- The subject has other serious comorbidities that will limit his or her ability to complete the study.

Main Criteria for Evaluation and Analyses:

The primary endpoints for this study are PK parameters at Week 14 (area under the serum concentration-time curve at Week 14 [$AUC_{Wk\ 14}$], average serum concentration during a dosing interval at Week 14 [$C_{av,Wk\ 14}$], and observed serum concentration at the end of Week 14 [$C_{trough,Wk\ 14}$]).

The secondary endpoints for this study are:

- Percentage of UC subjects who achieve clinical response based on complete Mayo score at Week 14.
- Percentage of CD subjects who achieve clinical response based on CDAI, as defined by a ≥70 point decrease from baseline in CDAI score at Week 14.

Statistical Considerations:

The PK parameters will be derived by compartmental and/or noncompartmental approaches, data permitting. All PK parameters will be summarized using descriptive statistics (nonmissing values, mean, SD, percent coefficient of variation [%CV], median, minimum, maximum) by dose and weight group.

All proportion-based efficacy endpoints will be summarized by presenting the point estimate and 95% CIs for the proportion by indication (UC or CD) and dose group. Subject with any component of a scale missing will be considered as a nonresponder/nonremitter for that particular endpoint, scale, or time point in the analysis.

Sample Size Justification:

The planned sample size is approximately 80 subjects including 40 subjects who weigh ≥30 kg and 40 subjects who weigh <30 kg. Subjects will be randomly assigned in a 1:1 ratio to receive 1 of 2 dose regimens (high or low) per weight group (≥30 kg or <30 kg). The randomization will be stratified by previous exposure/failure to TNF-α antagonist therapy or naive to TNF-α antagonist therapy and by indication (UC or CD) and by weight group (≥30 kg or <30 kg). Randomization caps will be implemented to ensure that the sample size for each dose regimen will be a minimum of 9 subjects with UC and 9 subjects with CD per weight group. A sample size of 9 subjects is expected to have at least 80% power to establish 95% CIs that are within 60% and 140% of the geometric mean estimates for total clearance after IV administration (CL) for each dose (high or low), indication (UC or CD), and weight group (≥30 kg or <30 kg), assuming the intersubject variability for CL in the pediatric population is similar to that in the adult population (%CV ≤36.6%). The sample size is based on industry guidance; CL is used because it controls overall drug exposure (area under the serum concentration-time curve [AUC] and average serum concentration during a dosing interval) and it is the parameter that allows computation of the dosage required to maintain an average steady-state concentration. The proposed sample size will also allow for descriptive analysis of efficacy for each indication and characterization of the dose-response relationship in pediatric subjects.

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

3.2 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

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{Wk\ 14}$	area under the serum concentration-time curve at Week 14
CCI	[redacted]
AZA	azathioprine
bpm	beats per minute
$C_{av,Wk\ 14}$	average serum concentration during a dosing interval at Week 14
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
C difficile	*Clostridium difficile*
CFR	Code of Federal Regulations
CL_L	linear total clearance
CL	total clearance after IV administration
CMV	cytomegalovirus
C_{trough}	serum concentration at the end of a dosing interval
$C_{trough,Wk\ 14}$	serum concentration at the end of Week 14
$C_{trough,Wk\ 22}$	serum concentration at the end of Week 22
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
ET	Early Termination
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal(ly)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAC	Independent Adjudication Committee
IBD	inflammatory bowel disease

Term	Definition
IBDU	inflammatory bowel disease unclassified
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous(ly)
IRT	interactive web response technology
LFT	liver function test
LLN	lower limit of normal
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MLN0002	vedolizumab
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PCDAI	Pediatric Crohn's Disease Activity Index
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PTE	pretreatment event
PUCAI	Pediatric Ulcerative Colitis Activity Index
Q2W	once every 2 weeks
Q4W	once every 4 weeks
Q8W	once every 8 weeks
RAMP	Risk Assessment and Minimization for PML
SAE	serious adverse event
SAP	statistical analysis plan
SES-CD	simple endoscopic score for Crohn's disease
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal
VCAM-1	vascular cell adhesion molecule-1
WBC	white blood cell

3.4 Corporate Identification

TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.

TDC	TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Asia, TDC Europe and/or TDC Americas, as applicable

3.5 Study Definitions

Term	Definition
Ulcerative Colitis (UC) Subjects:	
Clinical response based on complete Mayo score or partial Mayo score	A reduction in complete Mayo score of ≥3 points and ≥30% from Baseline (or a partial Mayo score of ≥2 points and ≥25% from Baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
Clinical remission based on complete Mayo score	A complete Mayo score of ≤2 points with no individual subscore >1.
Clinical response based on PUCAI	A ≥20-point decrease from Baseline in Pediatric Ulcerative Colitis Activity Index (PUCAI) score.
Clinical remission based on PUCAI	PUCAI score <10.
Disease worsening	An increase in the PUCAI of >20 points at 2 consecutive visits at least 7 days apart, or the PUCAI was >35 points at any scheduled or unscheduled visit.
Crohn's Disease (CD) Subjects:	
Clinical response based on CDAI	A ≥70-point decrease from Baseline in Crohn's Disease Activity Index (CDAI) score.
Clinical remission based on CDAI	CDAI score ≤150.
Clinical response based on PCDAI	A ≥15-point decrease from Baseline in PCDAI score with total PCDAI ≤30.
Clinical response based on SES-CD	A ≥50% reduction in simple endoscopic score for Crohn's disease (SES-CD) score from Baseline endoscopy (or meets criteria for clinical remission based on SES-CD score 0 to 2) with accompanying decrease in average daily abdominal pain score (CDAI component) by >0.25.
Clinical remission based on PCDAI	PCDAI score ≤10.
Enhanced clinical response based on CDAI	A ≥100-point decrease from Baseline in CDAI score.
Disease worsening	An increase in the PCDAI of >15 points at 2 consecutive visits at least 7 days apart, or the PCDAI was>30 points at any scheduled or unscheduled visit.

4.0 INTRODUCTION

4.1 Background

4.1.1 Epidemiology of UC and CD in the Pediatric Population

The overall prevalence of UC in the adult and pediatric population is approximately 200 cases/100,000 persons in the United States and about 150 cases/100,000 persons in Western Europe [1-4]. As of 2009, the prevalence rate of UC in the pediatric population was 34/100,000 persons, with the lowest prevalence rate being observed in children younger than 5 years [5]. Although in recent years the UC incidence has increased in the age group of 11 to 15 years, this rate has remained stable in children younger than 10 years [6]. No significant differences in prevalence by sex have been reported for pediatric UC [5]. However, a family history of UC does not seem to be a negative prognostic factor in UC patients [6].

In the United States, the overall prevalence of CD is approximately 125 cases/100,000 of the population and 150 cases/100,000 in Western Europe [1-4]. As of 2009, the prevalence rate of CD in children was 58/100,000 persons, with the lowest prevalence rate being observed in children younger than 5 years. Approximately 20% of all cases of CD occur in the pediatric population younger than 15 years, and a male preponderance is reported in pediatric CD [5], while a female preponderance is seen only among patients diagnosed during adolescence (13 to 19 years) [7].

A large study in the United States demonstrated that UC, CD, and indeterminate colitis (otherwise known as inflammatory bowel disease unclassified [IBDU]) were equally prevalent in the pediatric population up to 2 years of age and that definitive diagnoses were made in only 1% of patients before 1 year of age [8]. UC was the most prevalent disease type (47%) among those in the 3- to 5-year age group compared with CD (35%). The prevalence of indeterminate colitis decreased as children aged. A family history of inflammatory bowel disease (IBD) was noted in 3% of siblings, 9% of parents, and 22% of second-degree relatives, with the strongest family histories noted in the younger pediatric population and those with UC (44%). Although there are fewer studies of childhood IBD compared with adult-onset IBD, the pediatric population is unique in that there are fewer environmental confounders, such as smoking or contraceptive use, compared with adults. It is therefore possible that genetics and microbiology play a stronger role in the development of pediatric IBD. Compared with adult CD, pediatric CD appears to be associated with a higher frequency of mutation in the NOD2/CARD15 gene[7].

The incidence of pediatric IBD appears to be increasing. A large study in Finland showed a near doubling of the pediatric IBD incidence over a 15-year period [9,10]. In 1987, the incidence was 3.9 cases/100,000 of the population and increased to 7.0 cases/100,000 of the population in 2003. The highest frequency of new-onset cases in the pediatric population (33%) occurred in patients between age 12 and 15 years; however, 5% of cases occurred in children younger than 3 years. According to the Crohn's and Colitis Foundation of America, approximately 1 million Americans have either UC or CD, of which approximately 100,000 are younger than 21 years.

4.1.2 Clinical Manifestations and Prognosis of UC and CD in Pediatric Patients

Although UC and CD are separate illnesses, they share many common signs and symptoms. In both the pediatric and adult populations, clinical manifestations include diarrhea, abdominal pain, fecal urgency, and incontinence. Fever, weight loss, malaise, and fatigue are indicators of more extensive disease. There are a number of extraintestinal manifestations of IBD, including arthropathy, primary sclerosing cholangitis, and uveitis. For approximately 25% of IBD patients, the onset of disease occurs during childhood or adolescence. The diagnosis of UC or CD is usually established histopathologically via endoscopic mucosal biopsies in both adult and pediatric populations.

Disease localization appears to be affected by age. In CD, the most commonly affected sites in the pediatric population are the terminal ileum (71% of patients at diagnosis) and right colon (71%) [11]. Upper gastrointestinal (GI) involvement also is commonly seen in pediatric CD, although this may be a function of routine upper GI endoscopy with biopsies being routinely performed based upon consensus diagnostic recommendations [12]. In pediatric CD, simple inflammatory disease, which is predominant at diagnosis, appears to give way to complex stricturing and penetrating behavior over time.

In UC, the extent of disease at diagnosis is more widespread in the pediatric population compared with adults; pancolitis occurs in up to 90% and proctitis in only a minority of patients (4% to 13%). Rectal sparing may occur in only 30% of pediatric patients with UC and, therefore, unlike adults, sigmoidoscopy alone may be sufficient to establish the diagnosis in the pediatric population [7].

While the symptoms of UC are similar in both the pediatric and adult populations, pediatric patients usually present with more extensive disease. Less is known about the clinical course of long-term disease [13]. Whether the course differs in children, adolescents, and adults is unknown at present [7]. Antineutrophil cytoplasmic antibody and anti-Saccharomyces cerevisiae antibody serologies have been associated with a greater risk of developing earlier and more frequent complications in pediatric CD [14] and may serve as a useful stratification variable in therapeutic trials of CD.

Although growth failure is a common sequela of UC and CD in the pediatric population, pediatric patients with CD appear to be at twice the risk of growth failure compared with those with UC [15]. Nutritional therapy and surgical resection have been shown to improve growth, but there remains a clear need for more effective and less morbid treatment options. As with adults, long-term complications of UC and CD in pediatric patients include malignancy (eg, colorectal cancer), which may be attributable at least in part to the underlying inflammatory disease and also possibly to treatment with systemic immunosuppressants.

Treatment options for adult and pediatric patients are similar. Pharmacological treatments for these diseases include the 5-aminosalicylic acid (5-ASA) and its derivatives, corticosteroids, and immunomodulators (thiopurines, such as azathioprine [AZA] and 6-mercaptopurine [6-MP]) for both UC and CD, along with methotrexate (MTX) for CD. AZA and 6-MP are often used in conjunction with corticosteroids or other therapy to induce remission. AZA and 6-MP show efficacy in maintaining remission in pediatric CD [16] and also in moderate to severe pediatric UC

[17]. MTX has a rapid onset of action and has been shown to be effective in induction and maintenance of remission in pediatric patients with CD [18-20]. Over the past decade, tumor necrosis factor-alpha (TNF-α) antagonist therapies have been studied and approved for use in the pediatric population. Infliximab is approved for use in pediatric patients with moderately to severely active UC or CD in the United States and European Union [21], and adalimumab is approved in the United States and European Union for moderately to severely active CD [22].

4.1.3 Vedolizumab IV

Vedolizumab (also known as MLN0002) is a recombinant humanized monoclonal antibody composed of 2 light chains of the κ subclass and 2 immunoglobulin G1 heavy chains. Vedolizumab binds specifically to the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [23-26]. As a result, vedolizumab impairs the migration of gut-homing leukocytes into GI mucosa [27] and acts as a gut-selective immunomodulator.

Vedolizumab IV (also known as ENTYVIO; KYNTELES; Vedolizumab for Injection, for Intravenous Use; Vedolizumab Powder for Concentrate for Solution for Infusion, or MLN0002 IV) has been granted marketing approval in over 50 countries, including the United States and European Union, for the treatment of adult patients with moderately to severely active UC or CD who have failed conventional treatment, including immunomodulators, corticosteroids, or TNF-α antagonists. The approved initial dose and administration regimen consists of 300 mg vedolizumab IV infused intravenously (IV), over approximately 30 minutes, at Day 1 and Weeks 2, 6, and then once every 8 weeks (Q8W) thereafter.

4.1.3.1 Nonclinical

Extensive nonclinical evaluations of the cardiovascular, acute, local tolerance, subchronic, chronic, immunologic, and reproductive toxicity in pharmacologically responsive species (New Zealand white rabbits and cynomolgus monkeys) have been conducted with vedolizumab. In local tolerance studies in rabbits, no evidence of significant adverse local effects was seen following administration of vedolizumab IV or vedolizumab subcutaneous. No evidence of effects on electrocardiogram (ECG), heart rate, or mean arterial pressure was seen in cynomolgus monkeys at vedolizumab doses up to 100 mg/kg. In addition, there was no evidence of embryo-fetal toxicity (gravid rabbits) or prenatal and postnatal toxicity (cynomolgus monkeys), or immunotoxicity (cynomolgus monkeys) at these doses. The no-observed-adverse-effect level (NOAEL) in both pharmacologically responsive species (monkeys and rabbits) was vedolizumab 100 mg/kg. This dose was associated with an exposure 26 times (rabbits) and 18 times (cynomolgus monkeys) higher than the geometric mean clinical area under the serum concentration-time curve (AUC) after a single dose of vedolizumab 300 mg IV by 30-minute infusion.

A 13-week toxicity study of vedolizumab IV in juvenile cynomolgus monkeys (11 to 15 months old at study start) supports studies in the pediatric population. Monkeys of this species typically

are weaned at around 9 months old, making the specified ages of the monkeys equivalent to young children, although an exact age correspondence cannot be defined. Juvenile monkeys were dosed with the same dose regimen as previously studied in adult monkeys (approximately 3 to 7 years old): 0 (vehicle control), 10, 30, or 100 mg/kg administered by 30 minute IV infusion once every 2 weeks (Q2W). There were no test article-related clinical observations, or effects on body weights, food consumption, ophthalmology, electrocardiology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), T-cell–dependent antibody response, flow cytometry analyses (peripheral blood and cerebrospinal fluid), macroscopic and microscopic findings, and organ weights. Thus, 100 mg/kg was considered to be the NOAEL in this study.

4.1.3.2 Clinical

No studies have been completed in pediatric subjects. Data are not yet available for studies being conducted in Japan that will include subjects ≥15 years. Single- and multiple-dose pharmacokinetics (PK) of vedolizumab IV have been studied in healthy adult subjects and in subjects with moderately to severely active UC or CD. Similar vedolizumab PK was observed in healthy subjects and subjects with UC or CD. In adults, vedolizumab serum concentrations generally fell in a biexponential fashion until approximately 1 to 10 µg/mL, with a total clearance after IV administration (CL) of approximately 0.157 L/day and a serum half-life of around 25 days. Thereafter, the serum concentrations fell in a nonlinear fashion. The volume of distribution for vedolizumab IV is approximately 5 L.

Vedolizumab IV has demonstrated statistically significant and clinically relevant evidence of effectiveness in multiple completed clinical studies in adult subjects with moderately to severely active UC or CD.

In subjects with moderately to severely active UC (C13006; GEMINI I), vedolizumab IV 300 mg administered as an IV infusion at Day 1 and Week 2 (induction) followed by either Q8W or once every 4 weeks (Q4W) administration from Week 6 through Week 52 (maintenance) induced a statistically significant increase in rates of clinical response at Week 6 and clinical remission at Week 52 (primary endpoint for the induction phase and maintenance phase, respectively) compared with placebo [28]. The study also met important secondary endpoints, including clinical remission at Week 6, durable clinical response, durable clinical remission, and mucosal healing at Weeks 6 and 52, and corticosteroid-free clinical remission at Week 52. Given the significant morbidity associated with chronic corticosteroid treatment, the corticosteroid-sparing effects of vedolizumab provide an important benefit to patients with UC.

In subjects with moderately to severely active CD (C13007; GEMINI II), vedolizumab IV 300 mg administered as an IV infusion at Day 1 and Week 2 (induction) followed by either Q4W or Q8W administration from Week 6 through Week 52 (maintenance) demonstrated statistically significant differences in efficacy compared with placebo for both the induction phase and maintenance phase [29]. The study met its first 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 met 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.

In C13011 (GEMINI III), vedolizumab (300 mg IV at Day 1 and Weeks 2 and 6) was administered as induction therapy to subjects with moderately or severely active CD who had failed conventional therapies, including TNF-α antagonists. The primary endpoint of clinical remission at Week 6 in the TNF-α antagonist failure intent-to-treat population was not met; however, a treatment difference was observed at Week 10 in this population [30]. Similar treatment differences favoring vedolizumab were also demonstrated for the overall population and in the subgroup of subjects who were TNF-α antagonist naïve.

Vedolizumab has shown an acceptable safety profile based on an analysis of safety data from both completed and ongoing studies, as well as from postmarketing experience (see current version of Investigator's Brochure). Vedolizumab was well-tolerated in phase 1 and 2 clinical studies. The majority of the safety data is from 3 well-controlled, phase 3 clinical studies that evaluated the safety of vedolizumab for up to 12 months in subjects with UC (Study C13006 [52 weeks]) or CD (Studies C13007 [52 weeks] and C13011 [10 weeks]). Subgroup analyses based on weight did not show any clinically relevant differences from the overall safety population. In addition, an interim safety assessment is available for an ongoing, uncontrolled long-term extension study (Study C13008), in which subjects are administered vedolizumab Q4W.

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

In the pivotal phase 3 studies (Studies C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most serious adverse events (SAEs) were 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 correlate with the known tissue distribution of MAdCAM-1 binding sites. Anal abscess, abdominal abscess, and gastroenteritis were the most frequently reported serious infections. Extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis) occurred at low frequency (<1%). Concomitant use of corticosteroids and/or conventional immunomodulators did not appear to be associated with any increased rate of infections based on the comparative rates of infections in the phase 3 clinical studies among subjects. Results from the clinical program to date do not suggest an increased risk of malignancy with vedolizumab IV treatment. No cases of progressive multifocal leukoencephalopathy (PML) were reported in these studies or during postmarketing experience to

date. A similar safety profile was observed in adult subjects who received vedolizumab IV Q8W or Q4W.

Overall, 4% of subjects treated with vedolizumab IV and 3% of subjects treated with placebo experienced a treatment-emergent adverse event (TEAE) defined by the investigator as an infusion-related reaction (IRR). The most frequently observed IRR events in the subjects treated with vedolizumab (by preferred term and reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, IRR, pyrexia, urticaria, and vomiting. The majority of IRRs were mild or moderate in intensity, and few resulted in discontinuation of study treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion.

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

Overall, vedolizumab was well tolerated in clinical studies and postmarketing safety data are consistent with the safety profile observed in the clinical studies. The benefit/risk profile continues to be positive.

4.2 Rationale for the Proposed Study

A safe and effective dose for vedolizumab in children has yet to be determined. The aim of this phase 2 dose-ranging study is to evaluate vedolizumab PK in male and female pediatric subjects with moderately to severely active UC or CD. In addition, the dose-response at Week 14 in these subjects will be characterized to aid in dose selection for the pediatric phase 3 studies. PK, efficacy (including endoscopic assessment at Week 14), and safety assessments will be performed during the 22-week study.

Eligible subjects will be randomized to receive doses of vedolizumab IV by infusion at Day 1 and Weeks 2, 6, and 14 as follows:

- Subjects weighing ≥30 kg:
  - Vedolizumab IV 300 mg (high dose).
  - Vedolizumab IV 150 mg (low dose).
- Subjects weighing 10 kg to <30 kg:
  - Vedolizumab IV 200 mg (high dose).
  - Vedolizumab IV 100 mg (low dose).

4.3 Benefit/Risk Assessment

Since vedolizumab has not yet been formally evaluated in pediatric subjects, the benefit/risk profile in pediatric patients with UC or CD has not been determined. Ongoing studies being conducted in Japan will include subjects ≥15 years of age; however, data are not yet available in these adolescent subjects.

There remains an unmet medical need in pediatric patients who fail to respond, or who lose response to, all existing therapy (including conventional therapy or TNF-α antagonists), or in whom side effects of these agents are intolerable or life threatening. Vedolizumab IV may provide an alternative therapy for this patient population.

Vedolizumab IV has demonstrated statistically significant and clinically relevant evidence of effectiveness in multiple completed clinical studies in adult subjects with moderately to severely active UC or CD.

In clinical studies, vedolizumab has shown an acceptable and consistent safety profile in adults (≥18 years of age) with body weights ranging from 28.7 kg to 170 kg. In the pivotal phase 3 studies in adult UC and CD subjects (C13006 and C13007), the most common (≥5% and at a higher incidence than placebo) adverse reactions in subjects administered vedolizumab IV were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, and cough. Most 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. No additive risk of infection was identified among subjects who received a concomitant immunosuppressant. A similar safety profile was observed in adult subjects who received vedolizumab IV Q8W or Q4W. Postmarketing safety has been consistent with the safety profile observed during clinical development.

In addition, results from a 13-week juvenile monkey toxicity study showed that vedolizumab was safe and well tolerated at doses up to 100 mg/kg, which was the highest dose tested. Thus, based on the clinical and postmarketing data in adults, combined with nonclinical data in juvenile monkeys, the benefit/risk profile in pediatric subjects with UC or CD is expected to be positive.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate vedolizumab PK in pediatric subjects with UC or CD.

5.1.2 Secondary Objectives

- To assess the efficacy of vedolizumab IV in pediatric subjects with UC or CD.
- To characterize the dose-response relationships of vedolizumab IV in pediatric subjects with UC or CD.

5.1.3 Additional Objectives

- To assess the safety and tolerability of vedolizumab IV in pediatric subjects with UC or CD.

CCI [redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

PK parameters:

- Area under the serum concentration-time curve at Week 14 ($AUC_{Wk\ 14}$).
- Average serum concentration during a dosing interval at Week 14 ($C_{av,Wk\ 14}$).
- Observed serum concentration at the end of a dosing interval at Week 14 ($C_{trough,Wk\ 14}$).

5.2.2 Secondary Endpoints

- Percentage of UC subjects who achieve clinical response based on complete Mayo score, as defined by a reduction in complete Mayo score of ≥3-points and ≥30% from Baseline with an accompanying decrease in rectal bleeding subscore of ≥1-point or absolute rectal bleeding subscore of ≤1-point at Week 14.
- Percentage of CD subjects who achieve clinical response based on CDAI, as defined by a ≥70-point decrease from Baseline in CDAI score at Week 14.

5.2.3 Additional Endpoints

CCI [redacted]

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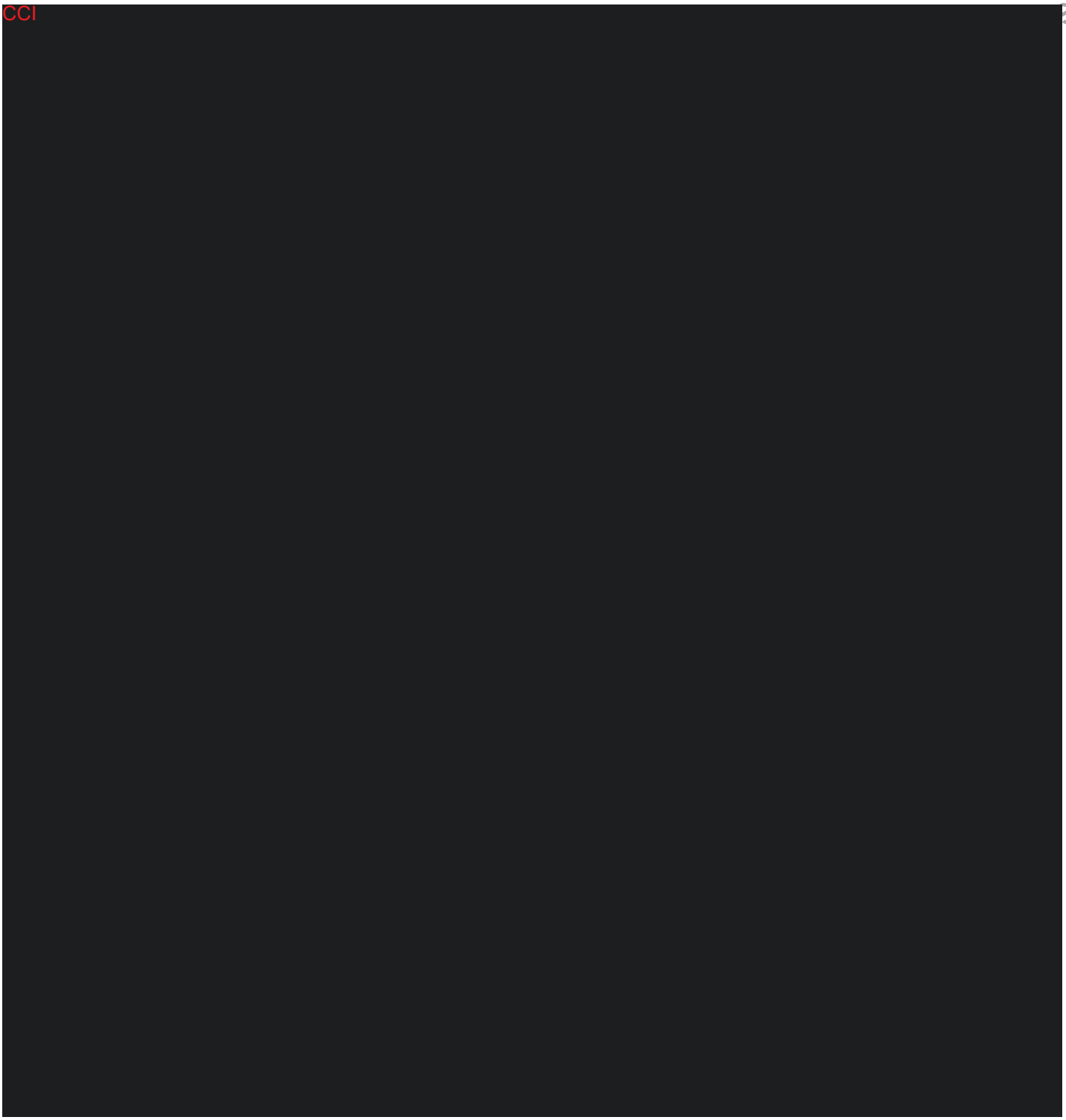

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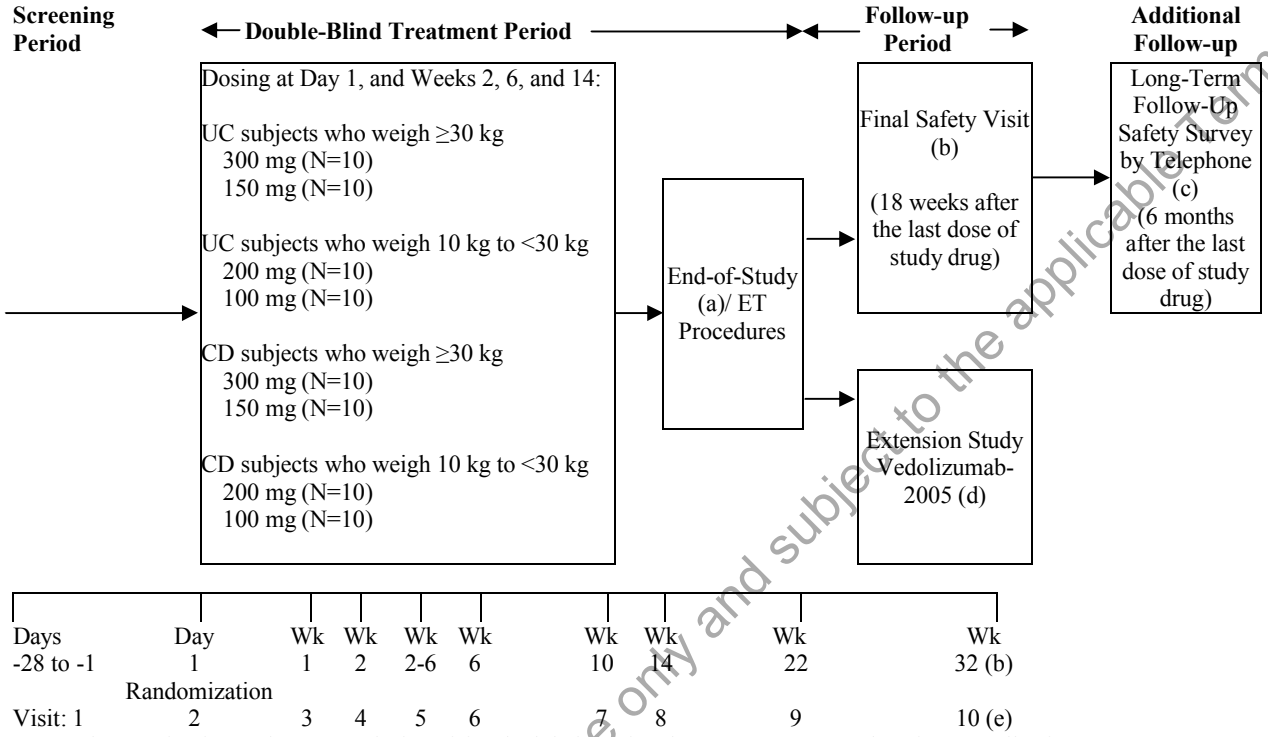
6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2, randomized, double-blind, dose-ranging study involving pediatric subjects with moderately to severely active UC or CD who have demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents: corticosteroids, immunomodulators, and/or TNF-α antagonist therapy. The study will evaluate the PK, efficacy, immunogenicity, safety, and tolerability of vedolizumab IV. Approximately 80 pediatric subjects will be enrolled to ensure that 40 subjects weighing ≥30 kg and 40 subjects weighing 10 kg to <30 kg, as well as a minimum of 36 subjects with UC and a minimum of 36 subjects with CD, will be enrolled in the study. Subjects who discontinue may be replaced as determined by the sponsor.

This study includes a 4-week Screening Period, a 22-week Double-Blind Treatment Period (with last dose at Week 14) for all subjects. Eligible subjects may exit the study at Week 22 and continue to receive study drug in an extension study. Subjects who do not enter the extension study will participate in an 18-week Follow-up Period starting from the last dose of study drug and complete a long-term follow-up safety survey by telephone 6 months after their last dose of study drug. A schematic of the study design is included in Figure 6.a.

Figure 6.a Schematic of Study Design



ET=Early Termination, Wk 2-6=nondosing visit scheduled anytime between Days 16 and 42 for PK collection.
(a) Subjects who consent to participate in the extension study (Vedolizumab-2005) may be eligible for the extension study dosing after procedures have been completed at Week 22 (Visit 9).
(b) Subjects who do not enter the extension study or withdraw before Week 22 will also complete ET Visit (Week 22) procedures and a Final Safety Visit 18 weeks after their last dose of study drug.
(c) Subjects who withdraw before Week 22 will also participate in a long-term follow-up safety survey by telephone 6 months after the last dose of study drug.
(d) Subjects will provide informed consent/pediatric assent for participation in extension Study Vedolizumab-2005 on or after Week 14 through Week 22 of Study MLN0002-2003.Visit 1 of extension Study Vedolizumab-2005 is within 1 week of completing Week 22 (Visit 9) procedures.
(e) Subjects who do not enter the extension study (Vedolizumab-2005) will complete the Final Safety Visit 18 weeks after their last dose of study drug and participate in a long-term follow-up safety survey by telephone 6 months after the last dose of study drug.

The total duration of the study will be approximately 36 weeks from start of the Screening Period to the posttreatment Final Safety Visit. Study drug will be administered on Day 1 and Weeks 2, 6, and 14 as described in Section 8.1.3. Clinical response will be assessed at Week 14 based on PUCAI/PCDAI and recorded in the interactive web response technology (IRT) system. Subjects randomized to the low dose group who have not achieved clinical response will be escalated to receive the high dose of vedolizumab IV (300 mg for subjects ≥30 kg and 200 mg for subjects <30 kg) at Week 14. This blinded dose escalation will be done via IRT. Subjects randomized to the high dose group who have not achieved clinical response will continue on the same blinded dose at Week 14. At the Week 22 Visit, subjects may be eligible to enter an extension study (Vedolizumab-2005) to continue receiving study drug. Subjects who do not enter the extension study will complete an End-of-Study/ET Visit at Week 22 and then attend the Final Safety Visit 18

weeks after their last dose of study drug. Subjects who withdraw prior to Week 22 (ET) will complete the Week 22 assessments (and an endoscopy if prior to the Week 14 Visit) at their ET Visit and then attend the Final Safety Visit 18 weeks after their last dose of study drug. An ET endoscopy is not required for subjects who withdraw prior to Week 6. All subjects who do not participate in the extension study will also be required to participate in a long-term follow-up safety survey by telephone, 6 months after their last dose of study drug.

Eligible subjects will be randomly assigned in a 1:1 ratio to receive 1 of 2 dose regimens (high or low) per weight group on Day 1. The randomization will be stratified by previous exposure/failure to TNF-α antagonist therapy or naive to TNF-α antagonist therapy, by indication (UC or CD), and by weight group (≥30 kg or <30 kg). Randomization caps will be implemented to ensure the sample size for each dose regimen will be a minimum of 9 UC subjects and 9 CD subjects per weight group (≥30 kg or <30 kg).

A Schedule of Study Procedures is provided in Appendix A. Safety and efficacy assessments will be made throughout the study, at the Week 22 End-of-Study/ET Visit, and at the Final Safety Visit 18 weeks after the last dose of study drug (for subjects who do not enroll in the Vedolizumab-2005 extension study). SAEs and AEs will be collected throughout the study. Subjects will receive their last dose of study drug at Week 14 and have an endoscopy at the Week 14 Visit for efficacy evaluation.

Blood samples to evaluate PK will be collected (predose and/or postdose) over the course of the study as described in Section 9.1.12. CCI [redacted]).

6.1.1 Extension Study Vedolizumab-2005

Subjects who are eligible to enroll in Study Vedolizumab-2005 include those who, at Week 22 of Study MLN0002-2003, achieved clinical response as defined by a reduction of partial Mayo score of ≥2 points and ≥25% from Baseline, or a reduction of the PUCAI of ≥20 points from Baseline for subjects with UC; or a reduction of the CDAI as defined by a ≥70 point decrease from Baseline or a decrease of the PCDAI of ≥15 points for subjects with CD.

Subjects who elect to participate in Study Vedolizumab-2005 will provide informed consent/pediatric assent for participation on or after Week 14 through Week 22 of Study MLN0002-2003. Relevant assessments from the Week 22 Visits of Study MLN0002-2003 will be used as the predose assessments for the extension study.

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Justification for Study Design and Endpoints

This is a phase 2, dose-ranging study enrolling male and female pediatric subjects (2 to 17 years, inclusive) with moderately to severely active UC or CD who have failed at least 1 conventional therapy and/or TNF-α antagonist therapy. The study will evaluate the PK, efficacy, immunogenicity, safety, and tolerability of vedolizumab IV in pediatric subjects.

The primary endpoints of $AUC_{Wk\ 14}$, $C_{trough,Wk\ 14}$, and $C_{av,Wk\ 14}$ were selected to obtain pediatric PK data, as it is expected that all subjects will have achieved steady-state drug concentrations. The secondary endpoint is the percentage of UC subjects who achieve clinical response at Week 14 based on Mayo score and percentage of CD subjects who achieve clinical response at Week 14 based on CDAI score, which are commonly used to evaluate patients with UC and CD, respectively. The 14-week time point is expected to be sufficient for the purpose of characterizing PK and the dose-response relationship. The secondary endpoints will allow characterization of efficacy to explore the dose-response relationship in pediatric subjects to aid dose selection for the phase 3 studies. This study will continue to Week 22 to explore steady-state serum vedolizumab concentration observed at the end of the dosing interval ($C_{trough,Wk\ 22}$).

6.2.2 Dose Justification

The approved dose and administration regimen of vedolizumab IV in adult subjects is 300 mg administered at Day 1 and Weeks 2, 6, and Q8W thereafter. Vedolizumab IV has demonstrated an adequate safety profile in adults over a wide range of single or multiple doses up to 10 mg/kg.

In this study, eligible pediatric subjects will be randomly assigned to receive 1 of 2 dose regimens at Day 1 and Weeks 2, 6, and 14 as follows:

- Subjects weighing ≥30 kg:
  - Vedolizumab IV 300 mg (high dose).
  - Vedolizumab IV 150 mg (low dose).
- Subjects weighing 10 kg to <30 kg:
  - Vedolizumab IV 200 mg (high dose).
  - Vedolizumab IV 100 mg (low dose).

The high and low doses in subjects who weigh ≥30 kg or 10 kg to <30 kg proposed for this study were selected based on simulations performed using a population PK model developed from phase 3 data in adult subjects with UC or CD. Population PK analyses suggest that while body weight is a predictor of linear total clearance (CL_L) and volume of the central compartment (V_c), the magnitude of the effect is not considered to be clinically relevant. Population PK analyses suggest that CL_L of vedolizumab is not affected by subject age. The doses selected provide estimated serum concentration at the end of a dosing interval (C_{trough}) values in pediatric subjects that are between the 5th and 95th percentiles of C_{trough} values observed in adults administered vedolizumab IV 300 mg at Weeks 0, 2, 6 and Q8W or Q4W in phase 3 studies. Body weights in the adult pivotal phase 3 studies ranged from 28.7 to 170 kg. No clinically meaningful differences in safety were observed in adult subjects across quartiles of body weight.

The high and low doses to be tested in this study differ 2-fold and are expected to characterize dose-response in pediatric subjects. This information will be used to select doses for the phase 3 studies in pediatric subjects with UC or CD. Subjects assigned to the low dose group who do not achieve clinical response (based on PUCAI/PCDAI) at Week 14 will receive the high dose of vedolizumab IV (300 mg if ≥30 kg or 200 mg if 10 kg to <30 kg) at Week 14.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk /benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- The data safety monitoring board (DSMB) recommends that the study should be suspended or terminated.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to first dose. Subjects who are screen failures may be rescreened, but will need prior approval by the sponsor.

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, parent, or legal guardian is capable of understanding and complying with protocol requirements.
2. The subject and/or the parent or legal guardian gives voluntary informed consent/assent and signs and dates a written informed consent/assent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject:
   a) is male or female; and
   b) weighs ≥10 kg at the time of randomization; and
   c) is 2 to 17 years, inclusive, at the time of randomization, with moderately to severely active UC or CD diagnosed at least 3 months prior to Screening by clinical and endoscopic evidence and corroborated by a histopathology report.
4. The subject has a medical history of moderately to severely active UC during Screening defined as a complete Mayo score of 6 to 12, and a total of Mayo subscores of stool frequency and rectal bleeding ≥4 and an endoscopy subscore ≥2; or has moderately to severely active CD defined as simple endoscopic score for Crohn's disease (SES-CD) ≥7, and the CDAI components of average daily Abdominal Pain Score of >1 for the 7 days prior, and total number of liquid/very soft stools >10 for the 7 days prior to the first dose of study drug.
5. The subject has evidence of UC extending proximal to the rectum (ie, not limited to proctitis) or evidence of CD involving the ileum and/or colon, at a minimum.
6. Subjects with extensive colitis or pancolitis of >8 years duration or left-sided colitis of >12 years duration must have documented evidence that a surveillance colonoscopy was performed within 12 months prior to their first dose of study drug.
7. A male subject who is sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent/assent throughout the duration of the study and for 18 weeks after last dose or agree to completely abstain from heterosexual intercourse.
8. 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/assent throughout the duration of the study and for 18 weeks after last dose or agree to completely abstain from heterosexual intercourse.

*Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

9. Subjects with a family history of colorectal cancer (ie, first-degree relative), personal history of increased colorectal cancer risk, or other known risk factor must be up-to-date on colorectal cancer surveillance.
10. The subject's vaccinations are up to date.
11. The subject has demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:

    Corticosteroids:

    - Signs and/or symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to or more than prednisone 1 mg/kg daily orally for 2 weeks or IV for 1 week.

    OR

    - Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions.

    OR

    - History of significant intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection).

    Immunomodulators

    - Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral AZA (≥1.5 mg/kg/day) or 6-MP mg/kg (≥1.0 mg/kg/day) or MTX (≥10 mg/m^2 once a week).

    OR

    - History of intolerance of at least 1 immunomodulator (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test (LFT) abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, infection).

    TNF-α antagonists

    - Signs and symptoms of persistently active disease despite a history of at least 1 induction regimen of infliximab 5 mg/kg IV at Week 0 and Weeks 2 and 6 or adalimumab 2-week regimen of 160 mg on Day 1 and 80 mg on Day 15 if ≥40 kg or 80 mg on Day 1 and 40 mg on Day 15 if <40 kg. For any other TNF-α antagonist, the subject must demonstrate signs and symptoms of persistently active disease despite a history of at least 1 induction regimen, as determined by the investigator.

OR

- Recurrence of symptoms during maintenance dosing following prior clinical benefit, ie, fitting clinically with secondary loss of response (discontinuation despite clinical benefit does not qualify).

OR

- History of intolerance of infliximab or adalimumab (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, infection).

12. The subject may be receiving a therapeutic dose of the following drugs:
    a) Oral 5-ASA compounds, providing the dose has been stable for the 2 weeks prior to first dose of study drug.
    b) Oral corticosteroid therapy (prednisone at a stable dose ≤50 mg/day, or equivalent steroid), provided that the dose has been stable for the 4 weeks prior to first dose of study drug if corticosteroids have been initiated, or for the 2 weeks prior to first dose of study drug if corticosteroids are being tapered.
    c) Probiotics (eg, Saccharomyces boulardii), provided the dose has been stable for the 2 weeks prior to first dose of study drug.
    d) Antidiarrheals (eg, loperamide, diphenoxylate with atropine) for control of chronic diarrhea.
    e) Antibiotics used for the treatment of CD (eg, ciprofloxacin, metronidazole), providing the dose has been stable for the 2 weeks prior to first dose of study drug.
    f) Azathioprine or 6-MP, provided the dose has been stable for the 8 weeks prior to first dose of study drug.
    g) MTX, provided the dose has been stable for the 8 weeks prior to first dose of study drug.

7.2 Exclusion Criteria

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

1. The subject has had previous exposure to approved or investigational anti-integrins including, but not limited to, natalizumab, efalizumab, etrolizumab, or AMG 181, or MAdCAM-1 antagonists, or rituximab.
2. The subject has had prior exposure to vedolizumab.
3. The subject has had hypersensitivity or allergies to any of the vedolizumab excipients.
4. The subject has received:
    a) any investigational biologic (other than those listed in Exclusion Criterion #1) within 60 days or 5 half-lives prior to Screening (whichever is longer).

b) an approved biologic or biosimilar agent within 2 weeks prior to the first dose of the study drug or at any time during the Screening period.

5. The subject has a positive PML subjective symptom checklist prior to the administration of the first dose of study drug.
6. The subject currently requires surgical intervention for UC or CD, or is anticipated to require surgical intervention for UC or CD during this study.
7. Within 30 days prior to first dose of study drug, the subject received any of the following for the treatment of underlying disease:
   a) Nonbiologic therapies (eg, cyclosporine, thalidomide) other than those specifically listed in Section 7.3.
   b) A nonbiologic investigational therapy.
8. Use of topical (rectal) treatment with 5-ASA or corticosteroid within 2 weeks of the administration of the first dose of study drug.
9. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at Screening.
10. The subject has any of the following laboratory abnormalities during the Screening Period:
    a) Lymphocyte count $<1.0\times10^9$/L or investigator concern regarding underlying lymphocytopenia.
    b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× the upper limit of normal (ULN).
    c) Alkaline phosphatase >3×ULN.
    d) Serum creatinine >2×ULN.
11. The subject has any unstable or uncontrolled cardiovascular, heart failure moderate to severe (New York Class Association III or IV), pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurological, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise subject safety.
12. Active or latent tuberculosis (TB), as evidenced by a diagnostic TB test performed within 30 days of Screening or during the Screening Period that is positive, defined as:
    - Positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, ***OR***
    - A TB skin test reaction ≥5 mm.
      NOTE: If subjects have received BCG vaccine then a QuantiFERON TB Gold test should be performed instead of the TB skin test.

    Note: subjects with documented previously treated TB with a negative QuantiFERON test can be included in the study.

13. Clinically significant current or recent history (within 1 year prior to signing of informed consent/assent) of alcohol dependence or illicit drug use.
14. The subject is required to take excluded medications listed in Section 7.3.
15. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 18 weeks after the last dose of study drug, or intending to donate ova during such time period. If male, the subject intends to donate sperm during the course of this study or for 18 weeks after the last dose of study drug.
16. The subject has a current diagnosis of indeterminate colitis (IBDU). For subjects less than 6 years of age, any findings that suggest monogenic very early onset inflammatory bowel disease should be excluded.
17. The subject has evidence of abdominal abscess or toxic megacolon at the Screening Visit.
18. The subject has ileostomy, colostomy, ileo-anal pouch, or known fixed symptomatic stenosis of the intestine.
19. The subject has extensive colonic resection, eg, subtotal or total colectomy.
20. The subject has a history or evidence of adenomatous colonic polyps that have not been removed.
21. The subject has a history or evidence of colonic mucosal dysplasia.
22. The subject has chronic hepatitis B virus (HBV) infection* or chronic hepatitis C virus (HCV) infection.

    * HBV immune subjects (ie, being hepatitis B surface antigen [HBsAg] negative and hepatitis B antibody positive) may be included, however.
23. The subject has any identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation).
24. The subject has evidence of or treatment for *Clostridium difficile (C difficile*) infection within 60 days or other intestinal pathogen within 30 days prior to first dose of study drug.
25. The subject has other serious comorbidities that will limit his or her ability to complete the study.
26. The subject has any history of malignancy, except for the following: (a) adequately treated nonmetastatic basal cell skin cancer; (b) squamous cell skin cancer that has been adequately treated and that has not recurred for at least 1 year prior to enrollment; and (c) history of cervical carcinoma in situ that has been adequately treated and that has not recurred for at least 3 years prior to first dose of study drug. Subjects with remote history of malignancy (eg, >10 years since completion of curative therapy without recurrence) will be considered based on the nature of the malignancy and the therapy received, and inclusion must be discussed with the sponsor on a case-by-case basis prior to enrollment.

27. The subject has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, or neurodegenerative disease.
28. The subject has active psychiatric problems that, in the investigator's opinion, may interfere with compliance with the study procedures. This includes affective disorders that may confound the interpretation of subject reporting of gastrointestinal symptoms (eg, abdominal pain) in the opinion of the investigator.
29. The subject had a clinically significant infection (eg, pneumonia, pyelonephritis) within 30 days prior to first dose of study drug.
30. The subject has received any live vaccinations within 30 days prior to first dose of study drug.
31. The subject has history of lupus.
32. The subject has had a surgical procedure requiring general anesthesia within 30 days prior to screening or is planning to undergo major surgery during the study period.
33. The subject is unable to comply with all study assessments.
34. The subject is an immediate family member or study-site employee, or is in a dependent relationship with a study-site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

7.3 Excluded Medications and/or Procedures, and Treatments

The following medications are excluded from use during the study:

- Any treatment for UC or CD other than those listed in Section 7.3.1 (either approved or investigational).
- All live vaccines during the study treatment period and for at least 6 months after the last dose of study drug.
- Either approved or investigational biological agents for the treatment of non-IBD conditions, other than localized injections (eg, intraocular injections for wet macular degeneration).
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use defined as daily use for >2 consecutive weeks (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps are permitted).
- TNF-α antagonists may not be administered after subject signs informed consent/assent to participate in the study.

Subjects must be instructed not to take any medications, including over-the-counter (OTC) products, without first consulting with the investigator.

7.3.1 Permitted Medications and Treatments

The following medications are permitted during the study:

- Immunomodulators (such as MTX, AZA, 6-MP), stable for at least 8 weeks prior to first dose of study drug.
- Oral 5-ASAs, probiotics, enteral nutrition, or antibiotics stable for at least 2 weeks prior to first dose of study drug.
- Antidiarrheals for control of chronic diarrhea. Any significant increase in the subject's use in the 2 weeks prior to first dose of study drug must be considered by the investigator.

Concomitant medications, with the exception of corticosteroids, must be maintained at a constant dose throughout the first 14 weeks of the study. Any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC or CD symptoms (other than antidiarrheals for control of chronic diarrhea) will need to be discussed with the medical monitor. Initiation of corticosteroids, immunosuppressants, or other therapies is not permitted during the study. Initiation of these therapies after the first dose of study drug will result in the subject being withdrawn from the study as a failure to respond to study drug. However, medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety.

7.3.1.1 Oral Corticosteroid Dosing

For subjects on corticosteroids whose dose is not being tapered during Screening, their dose must remain stable for at least the first 2 weeks after their initial dose of study drug.

Corticosteroid doses may be tapered during the screening period up until the final 2 weeks prior to the first dose of study drug when a stable dose must be maintained. The corticosteroid dose must also remain stable during the first 2 weeks of vedolizumab treatment during the study, for a total of 4 weeks of stable corticosteroid dosing.

After the Week 2 dose of study drug, tapering of the corticosteroid dose may be initiated at the discretion of the investigator:

- For subjects entering the study at a corticosteroid dose of ≥20 mg/day, tapering may resume by 5 mg/week down to 20 mg/day for subjects weighing ≥40 kg, and down to 0.5 mg/kg/day for those <40 kg.
- For subjects entering the study at a corticosteroid dose of <20 mg/day, tapering may resume by 5 mg/week down to 10 mg/day for those who weigh ≥40 kg or more and down to 0.25 mg/kg/day for those weighing <40 kg.

Once these thresholds are reached, the corticosteroid dose will be held stable until the third dose of study drug is given at Week 6. Thereafter, between Weeks 6 and 14, corticosteroid tapering may resume at the discretion of the investigator by 5 mg/week down to 10 mg/day, and thereafter by 2.5 mg/week until zero.

If the investigator decides not to taper corticosteroids, the maximum dose of oral corticosteroids for the treatment of UC or CD that may be coadministered with vedolizumab IV is ≤50 mg/day of prednisone (or equivalent steroid) as long as that dose has been stable for 2 weeks prior to the first dose of study drug. Subjects who require higher doses should be withdrawn from the study.

7.4 Diet and Fluid Control

There are no diet or fluid restrictions and subjects do not need to fast prior to study drug infusions or blood draws.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.20.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires ET 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 drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if the following circumstances occur at any time during study drug treatment:

     – ALT or AST >8×ULN, or

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

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

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

   - Leukopenia or lymphopenia: White blood cell (WBC) and lymphocyte counts will be monitored for all subjects. AZA, 6-MP, or MTX, if applicable, should be discontinued and the dose of vedolizumab held for an absolute lymphocyte count $<1.0\times10^9$/L at any point in the study. The absolute lymphocyte count must be repeated at appropriate intervals as determined by the investigator. The next dose of vedolizumab can be administered only if the absolute lymphocyte count is $\geq1.0\times10^9$/L. If the absolute lymphocyte count remains $<1.0\times10^9$/L, study drug should be discontinued and the subject withdrawn from the study.

2. PML:

   a) As described in Section 11.2.1 Risk Assessment and Management Program for PML (RAMP Program), vedolizumab will be held in subjects with a positive subjective PML

checklist. Subsequent doses of vedolizumab will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm.

b) Subjects with confirmed PML, as adjudicated by the PML Independent Adjudication Committee (IAC), will be withdrawn from the study.

3. Any serious infection that meets the following criteria:
   a) Life threatening as defined in Section 10.1.4.
   b) Requires intensive care unit admission.
   c) Systemic opportunistic infection including tuberculosis (including pulmonary), cytomegalovirus (CMV) (including CMV colitis), and listeriosis.
4. Significant protocol deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
5. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
6. 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).
7. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
8. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.
9. Death.
10. Other.

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

7.6 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 7.5 or if the investigator determines that discontinuation of the study drug is in the subject's best interest. In addition, a subject or subject's parent/legal guardian 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 Final Visit/ET Visit, the Final Safety Visit, and the 6 month long-term follow-up safety survey. Discontinued or withdrawn subjects may 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 sponsor will supply the study sites with the following study drug: vedolizumab IV 300 mg/vial, for single use in a 20 mL vial. CCI [redacted]. Each vial will be packaged in an appropriately labeled single-vial carton. The sponsor will only provide the study drug (vedolizumab). Sites will provide all other materials for infusion.

Each carton will have a single-panel or multilingual booklet label that will contain, but will not be limited to the following: sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, medication identification number, subject information, caution statement, directions for use, and storage conditions.

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

8.1.2 Storage

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

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

8.1.3 Dose and Regimen

The dose and dosing regimen for subjects in this study is provided in Table 8.a. All subjects will receive double-blind treatment of study drug by IV infusion on Day 1 and Weeks 2, 6, and 14. Subjects should remain on the doses assigned for their weight category at randomization on Day 1 (300 or 150 mg for subjects ≥30 kg; 200 or 100 mg for subjects 10 kg to <30 kg) even if their weight category changes during the study.

The infusion will be administered intravenously over approximately 30 minutes for all subjects weighing ≥20 kg (longer infusion times up to 60 minutes may be used). For subjects weighing <20 kg, the infusion will be administered over approximately 2 hours. 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.

Subjects assigned to the low dose group who do not achieve clinical response (based on PUCAI/PCDAI) at Week 14 will receive the high dose (ie, 300 mg for subjects ≥30 kg and 200 mg for subjects <30 kg) of vedolizumab IV at Week 14.

Table 8.a Dose and Regimen

Indication	Baseline Weight	Vedolizumab IV Dose	Treatment Description
UC	≥30 kg	300 mg (high dose) 150 mg (low dose)	IV infusion at Day 1 and Weeks 2, 6, and 14
	10 kg to <30 kg	200 mg (high dose) 100 mg (low dose)	
CD	≥30 kg	300 mg (high dose) 150 mg (low dose)	IV infusion at Day 1 and Weeks 2, 6, and 14
	10 kg to <30 kg	200 mg (high dose) 100 mg (low dose)	

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug to 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, to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

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

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

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to the appropriate regimen as described in Section 8.1.3.

The investigator or investigator's designee will access the IRT system at Screening to obtain the subject study number. The investigator or the investigator's designee will use the IRT to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. The medication identification (ID) number of the investigational drug to be dispensed will then be provided by the IRT. If sponsor-supplied drug is lost or damaged, the site can request a replacement from 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. The medication ID number of the investigational drug to be dispensed will be provided by the IRT.

8.3 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IRT.

8.4 Unblinding Procedure

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

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IRT.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF.

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed at the site. The site will maintain source documents in addition to entering data into the IRT.

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

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment in the 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 or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the medication ID used to prepare each dose.

- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

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

The investigator or designee must record the current inventory of all sponsor-supplied drugs in the IRT. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed, and the initials, seal, or signature of the person dispensing the drug.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction or destroyed at the site. Accountability for clinical trial material being destroyed at the site must be documented using a Study Accountability Tracking Document or equivalent document. In addition, a Certificate of Destruction document must be provided by the sites that can identify or allow traceability to the batches, and/or medication ID numbers involved, and actual quantities destroyed. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

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

A unique subject identification number (subject number) will be assigned to each subject at the time of Screening; this subject number will be used throughout the study.

Subjects reaching an age that is not covered by their pediatric assent must provide consent for their appropriate age group to remain in the study. Subjects who reach the age of consent must provide consent with a signed informed consent form to remain in the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained may include (depending on local regulations) date of birth or age, sex, Hispanic ethnicity (United States only), race as described by the subject or parent/guardian, 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 ongoing medical history.

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 1 month prior to signing of informed consent. Vaccination history does not need to be documented as medication history, and vaccination status will be recorded as part of the inclusion and exclusion criteria.

In addition, all prior biologic medication history for the treatment of UC or CD with the reason for discontinuation is to be collected for subjects where possible.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) GI system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and without shoes, socks, or hats. The Takeda standard for collecting weight is kilograms (kg) with 1 decimal place. Height should be recorded to the nearest tenth of a centimeter (if possible). Height may be measured using a wall-mounted stadiometer using replicated measurements (average of 3 measurements).

9.1.5 Vital Signs Procedure

Vital signs will include body temperature, respiratory rate, blood pressure, and pulse (beats per minute). On dosing days, vital signs are taken predose. Vital signs should be measured prior to any venesection/cannulation procedures.

9.1.6 Efficacy Measurements

9.1.6.1 Completion and Review of Entries to Diaries

During Screening, subjects and parents or legal guardians will be instructed on how to appropriately complete entries into the diary. Three days (UC) or 5 days (CD) of completed diary data prior to the Day 1 visit is required for disease activity index calculation. Data on disease activity collected during screening will be reviewed on Day 1, before administering the first dose of study drug to ensure that the subject is still eligible for inclusion. Scores between initial screening and Day 1 before dosing should not change substantially.

During the rest of the study, 7 days (UC) or 10 days (CD) of completed diary data prior to each visit is required for disease activity index calculation. Therefore, subject symptoms must be recorded daily throughout the study, including the Screening Period. Diary entries will be reviewed by site personnel during Screening and (prior to dosing, if applicable) at Day 1 and Weeks 1, 2, 6, 10, 14, and 22 (or ET Visit), and at any unscheduled visit(s) due to disease exacerbation. Subjects who enter the extension study (Vedolizumab-2005) will return their diaries to the site at the Week 22 Visit.

Entries should be reviewed and monitored by the study staff while the subject/parent or legal guardian is in the clinic, and any changes should be made directly onto the diary by the subject/parent or legal guardian. Diary entries will be transcribed by site personnel into the eCRF.

UC Activity

A PUCAI score (see Appendix E) will be evaluated using the subject's/parent's or legal guardian's paper diary entries collected during Screening and then at every scheduled visit during the study as per the Schedule of Study Procedures (Appendix A).

A complete Mayo score will be evaluated during Screening, using subject diary entries and flexible sigmoidoscopy results prior to randomization. A complete Mayo score will also be evaluated at Week 14 (prior to dosing) or an ET Visit (if appropriate). Subjects/parents or legal guardians will make daily entries into the diary, which will be used for Mayo score calculation.

During Screening, subjects/parents or legal guardians will be instructed on how to appropriately complete the daily diary entry. The symptoms of UC must be recorded throughout the study, including the Screening Period. Entries should be reviewed and monitored by the study staff while the subject/parent or legal guardian is in the clinic, and any changes should be made directly onto the diary by the subject/parent or legal guardian.

Diary entries preceding each study visit will be used to calculate the Mayo score. Because the flexible sigmoidoscopy preparation can interfere with the assessment of other clinical parameters, diary entries used to calculate the complete Mayo score should not be from days during which the flexible sigmoidoscopy preparation is administered.

A partial Mayo score will be derived at Day 1, Weeks 2, 6, 10, and 22, and at any unscheduled visit(s) due to disease exacerbation (see Appendix F).

CD Activity

A PCDAI score (see Appendix G) will be evaluated using the subject's/parent's or legal guardian's paper diary entries and laboratory results collected during Screening and then at every scheduled visit during the study as per the Schedule of Study Procedures (Appendix A).

A CDAI score (see Appendix H) evaluated during Screening using the subject/parent's or legal guardian's paper diary entries will also be derived at Day 1, Weeks 2, 6, 10, 14, and 22, and at any unscheduled visit(s) due to disease exacerbation. On all dosing days, the CDAI score components are to be performed prior to dosing; the total CDAI score will be calculated once results are available for all components. Entries should be reviewed and monitored by the study staff while the subject/parent is in the clinic, and any changes should be made directly onto the diary by the subject/parent.

Diary entries preceding each study visit will be used to calculate the CDAI score. Because the colonoscopy preparation can interfere with the assessment of other clinical parameters, diary entries used to calculate the complete CDAI score should not be from days during which the colonoscopy preparation is administered.

Further efficacy measurements will be made based on endoscopy using SES-CD score (see Appendix I).

9.1.7 Documentation of Concomitant Medications and Procedures

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject, parent, or legal guardian OTC. Concomitant medication is not provided by Takeda. A concomitant procedure is any nonpharmacological medical intervention to treat their UC or CD.

At each study visit (from signing of informed consent through the end of the study), subjects or parents/legal guardians will be asked whether they have taken any medication other than the study drug or undergone any procedures to treat their UC or CD. All medication (including vitamin supplements, OTC medications, and oral herbal preparations) and concomitant procedures must be recorded in the eCRF.

9.1.8 Use of Local Anesthetic

It is recommended to use local anesthetic patches (eg, Synera) or creams (eg, EMLA) for blood draws or IV insertions for the comfort of the subject. This will not be recorded as a concomitant medication.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood collected at any single visit (including blood collection for PK analysis) is approximately 13 mL for subjects weighing ≥30 kg and 8 mL for subjects weighing 10 to <30 kg. The approximate total volume of blood for the study is 86 mL for subjects ≥30 kg and 55 mL for subjects weighing 10 to <30 kg. Details of these procedures and required safety monitoring will be given in the laboratory manual. Clinical laboratory tests to be conducted are summarized in Table 9.a.

The central laboratory will perform laboratory tests for hematology and serum chemistries, with the exception of the urine pregnancy test, which will be performed at the study site, and the erythrocyte sedimentation rate (ESR), which may be performed at a local laboratory. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

Blood samples should be taken in the following order, so that PK samples are collected as close as possible to the scheduled nominal time point: PK, safety samples, CCI

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Please refer to Section 7.5 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 drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**
RBC	ALT
WBC with differential	Albumin
Hemoglobin	Alkaline phosphatase
Hematocrit	AST
Platelets	Direct bilirubin
INR (if required)	Total bilirubin
ESR	Total protein
	Creatinine
	Blood urea nitrogen
	Creatine kinase
	GGT
	Potassium
	Sodium
	Glucose
	Chloride
	Bicarbonate
	Calcium
	Amylase
	CRP
Other:	
Serum	**Urine**
HIV test Hepatitis panel, including HBsAg and anti-HCV QuantiFERON test CCI Female subjects only: Beta hCG (for pregnancy test; only collected at each scheduled visit for females who reach menarche prior to or during the study) (a)	Female subjects only: hCG (urine pregnancy test) (female subjects of childbearing potential; only collected at each scheduled visit for females who reach menarche prior to or during the study) (a)
Stool:	
C difficile testing and toxin A and B Fecal calprotectin Ova and parasite evaluation	

CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, GGT=γ-glutamyl transferase, hCG=human chorionic gonadotropin, RBC=red blood cell.
(a) Serum pregnancy analysis is performed at Screening Visit and Week 22/ET Visit. Urine pregnancy analysis is performed at all other scheduled visits as specified in Appendix A.

9.1.10 Contraception and Pregnancy Avoidance Procedure

9.1.10.1 Male Subjects and Their Female Partners

From signing of parental informed consent/assent form, throughout the duration of the study, and for 18 weeks after last dose of study drug, male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. 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 (Section 9.1.10.3).

9.1.10.2 Female Subjects and Their Male Partners

From signing of parental informed consent/assent form, throughout the duration of the study, and for 18 weeks after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below). In addition, they must be advised not to donate ova during this period. **This will apply to female subjects of childbearing potential who have reached menarche prior to or during the study.**

9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A female subject is considered a female subject of childbearing potential, that is, 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 post–bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, 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.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study 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:
  - 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. Standard-of-care medications and effective methods of contraception are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
3. 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.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent/assent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

5. During the course of the study, regular urine hCG pregnancy tests will be performed only for female subjects 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 male subjects with pregnant partners.
   c) Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in female subjects 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?
6. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), and a negative urine hCG pregnancy test prior to receiving any dose of study drug (as close as possible and prior to first dose of study drug, preferably on the same day).

9.1.11 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition to the procedures summarized below, the ET and follow-up procedures (ie, Final Safety Visit [18 weeks after the last dose of study drug] and the long-term follow-up safety survey by telephone [6 months after the last dose of study drug]) should be completed. Any pregnancies in the partner of a male subject during the study or for 18 weeks after the last dose of study drug should also be recorded, following authorization from the subject's partner.

If the pregnancy occurs during administration of active study drug or within 18 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1. The investigator must inform the subject of their right to receive treatment dose information. If the subject chooses to receive treatment dose information, the individual blind for dose should be broken by the investigator.

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

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

9.1.12 PK Sample Collection and Analysis

Blood samples for the assessment of PK will be collected as shown in the Schedule of Study Procedures (Appendix A). Blood samples (11 to 12 samples total) will be collected during the course of the study as follows:

- Day 1 (1 sample: postdose).
- Day 8 (Week 1) (1 sample; nondosing visit).
- Day 15 (Week 2) (2 samples: 1 predose and 1 postdose).
- Between Days 16 and 42 (Weeks 2 to 6) (1 sample; nondosing visit).
- Day 43 (Week 6) (2 samples: 1 predose and 1 postdose).
- Day 71 (Week 10) (1 sample; nondosing visit).
- Day 99 (Week 14) (2 samples: 1 predose and 1 postdose).
- Day 155 (Week 22) (1 sample).
  For subjects who continue to the extension study, the Day 155 (Week 22) PK sample should be predose to first dose of the extension study. For subjects who do not enroll into the extension study, the Day 155 (Week 22) PK sample should be collected anytime during the visit.
- Final Safety Visit 18 weeks after the last dose of study drug (for subjects who do not continue into the extension study).

Blood samples should be obtained within 30 minutes prior to dosing, where applicable, at Weeks 2, 6, and 14, and at any unscheduled visit for a subject who experiences a SAE or disease exacerbation. The exact dosing (start and end of infusion) and sampling times must be recorded accurately in the eCRF for all doses and PK samples. Samples collected outside the protocol times will not be considered to be protocol deviations as long as dosing (start and end of infusion) and PK sampling dates and time are accurately collected in the eCRF. If the infusion is stopped prematurely, this should be recorded in the eCRF and PK samples should be taken 5 minutes after the end of the infusion. The postdose samples collected on dosing days should be collected as close to the end of infusion as feasible (must be obtained within 60 minutes after the end of the infusion) from the opposite arm in which the study drug infusion was given. If blood collection from the opposite arm in which the study drug infusion was given is not feasible, the postdose sample may be collected from the infusion arm 30 to 60 minutes after the end of infusion and after the IV saline flush has been completed. Each blood sample will be aliquotted to provide 1 serum sample per time point. Detailed instructions on collection and processing of PK samples are included in the laboratory manual.

Serum concentrations of vedolizumab will be determined using validated sandwich enzyme-linked immunosorbent assay (ELISA).

9.1.13 Immunogenicity Sample Collection

CCI

[redacted]

9.1.14 TB Screening

All subjects will complete TB screening to determine eligibility. Subjects will be excluded from the study if they have active or latent TB, regardless of treatment history, as defined in Section 7.2.

9.1.15 Fecal Calprotectin Sample Collection

CCI

[redacted]

9.1.16 Stool Sample for Culture, Ova and Parasite Evaluation, and *C difficile* Assay

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

9.1.17 PML Checklist

Clinic staff will administer an age-appropriate version of 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, if applicable) 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 11.2.1. Vedolizumab will be held in subjects with a positive subjective PML checklist. Subsequent doses of vedolizumab will be administered only if the possibility of PML is definitively excluded, as described in the RAMP algorithm. Subjects with confirmed PML, as adjudicated by the PML IAC, will be withdrawn from the study.

The signs and/or symptoms from a positive PML checklist will be recorded as an AE. Additional information and tools for the RAMP can be found in the Study Manual.

9.1.18 IMPACT-III Questionnaire (Subjects 9 to 17 Years of Age)

The IMPACT-III questionnaire is a self-reported measure with 35 closed questions encompassing 6 domains: Bowel Symptoms (7 items), Systemic Symptoms (3 items), Social Functioning (12 items), Body Image (3 items), Treatment/Interventions (3 items), and Emotional Functioning (7 items). The IMPACT-III uses a 5-point Likert scale ranging from 1 to 5 for all answers. The outcome score ranges from 35 to 175, with higher scores suggesting better quality of life. IMPACT-III (where translations are available) will be administered to subjects aged 9 to 17 years at the time of first dose of study drug. Entries should be reviewed and monitored by the study staff while the subject/parent or legal guardian is in the clinic, and any changes should be made directly onto the questionnaire by the subject/parent or legal guardian. Questionnaire entries will be transcribed by site personnel into the eCRF.

After obtaining permission from the original authors to use the IMPACT-III questionnaire, the current version will be provided in the study manual.

9.1.19 Endoscopies

Endoscopy will be performed during Screening (unless 1 has already been performed within 28 days prior to signing of informed consent/assent) and at Week 14 (or ET Visit). This will involve a flexible sigmoidoscopy (sigmoidoscope) or a colonoscopy, performed with a videoendoscope following a cleansing preparation (oral or rectal cathartic). Endoscopies will be read centrally for the efficacy analysis, for the screening endoscopy, and for the Week 14 Visit endoscopy (or ET Visit if appropriate), wherever possible, through use of video recordings. An ET endoscopy is not required if a subject withdraws prior to Week 6. On the days that endoscopies are performed, all other study procedures for that visit should be performed either prior to the endoscopy or on another day within the visit window.

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent/assent.

If the subject is found to be not eligible at this 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.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.

- Study termination.
- Other.

Subject numbers assigned to subjects who fail screening should not be reused even if the subject is eligible to be rescreened. Subjects who are screen failures may be rescreened but need prior approval by the sponsor.

9.1.21 Documentation of Randomization

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

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

9.1.22 Monitoring Subject Treatment Compliance

Study drug will be administered in the clinic and treatment compliance will be monitored. If a subject is persistently noncompliant with the study drug (eg, fails to keep scheduled study visits), it may be appropriate to withdraw the subject from the study.

9.2 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).

9.2.1 Screening

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

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

9.2.2 Randomization and Stratification

Randomization will take place after confirmation of eligibility. Randomized subjects who do not complete the study may be replaced depending on emerging data from the ongoing study.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for the study, the subject should be randomized in the IRT, as described in Section 8.2. The randomization will be stratified by previous exposure/failure to TNF-α antagonists therapy or naive to TNF-α antagonists therapy, and by indication (UC or CD), and by weight group (≥30 kg or 10 kg to <30 kg). Subjects will be given the first dose of study drug as described in Section 6.1. The procedure for documenting screening failures is provided in Section 9.1.20.

9.2.3 End-of-Study or ET Visit

The End-of-Study Visit will be performed at Week 22 or at the ET Visit. The procedures listed in Schedule of Study Procedures (Appendix A) at Week 22 will be performed and documented. This is the End-of-Study for subjects entering the Vedolizumab-2005 extension study.

For all subjects that received study drug, the investigator must complete the End-of-Study eCRF page.

9.2.4 Final Safety Follow-up Visit

For subjects not participating in the Vedolizumab-2005 extension study, a Final Safety Follow-up Visit will be performed 18 weeks after the last dose of study drug. Assessments will be completed per the Schedule of Study Procedures (Appendix A) at the Final Safety Visit.

9.2.5 Long-term Follow-up Safety Survey

Upon completion or ET from the study, all subjects not entering the Vedolizumab-2005 extension study will be required to participate in a long-term follow-up safety survey by telephone 6 months after the last dose of study drug. This is the End-of-Study for subjects not entering the Vedolizumab-2005 extension study.

9.2.6 Poststudy Care

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

Subjects who complete the study through Week 22 may be eligible to enroll in an extension study and continue to receive vedolizumab IV.

9.2.7 Unscheduled Visits Due to Disease Exacerbation

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

- Physical examination (including height and weight).
- Vital signs assessment.
- Diary review.
- PML checklist.
- Collection of concomitant medications and procedures.
- Collection of AEs and SAEs.
- Clinical chemistry and hematology, as indicated.
- Stool sample for culture.
- Stool sample for fecal calprotectin.

- Urine hCG for female subjects of childbearing potential.
- PUCAI/PCDAI.
- CDAI score.
- Partial Mayo score.
- CCI [redacted]
- PK assessment.

There is no minimum time for repeat evaluation by unscheduled visit to determine if a subject meets the criteria for disease worsening (Section 3.5). In general, however, enough time should be provided for clinically meaningful change to occur (eg, 1 week).

9.2.8 Other Unscheduled Visits (if Applicable)

Subjects may return to the study center for unscheduled visits as needed. Unscheduled visits can be performed when the subject has a study-related issue in between regular visits (eg, SAE follow-up, LFT elevations). The following procedures may be done during these visits: concomitant medications, clinical laboratory blood draws, urine sample and AE collection, as appropriate. Standard-of-care visits (routine check-ups) should not be captured as an unscheduled visit in eCRF. However, if the visit is due to disease exacerbation, the procedures described in Section 9.2.7 should be performed.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) 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 or as an AE.

Laboratory values:

- Changes in laboratory values 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 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 ongoing medical history and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such an ongoing medical history, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic 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 ongoing medical history (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 drug, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs/serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

10.1.5 AESIs

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

10.1.6 Severity of PTEs and AEs

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

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

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

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

Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Drug

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

10.1.13 Outcome

- Recovered/resolved – the 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 are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study drug. Routine collection of AEs will continue until Week 22 (for subjects who enroll in the extension study) or until the Final Safety Visit, which is 18 weeks after the last dose of study drug (for subjects who do not enroll in the extension study).

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 or parents/legal guardians 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 be followed up for the purposes of the protocol.

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

a) Event term.

b) Start and stop date.

c) Severity.

d) Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).

e) Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.

f) Action concerning study drug (not applicable for PTEs).

g) Outcome of event.

h) Seriousness.

10.2.1.3 AE Collection Involving Medically Anticipated Clinical Events

UC and CD are associated with certain characteristic signs and symptoms, including diarrhea, rectal bleeding, and abdominal pain, that may be present at Baseline and persist or fluctuate based on the individual subject's disease history during the course of the study. These signs and symptoms will not be collected as AEs. These characteristics of disease activity will be regularly captured in the disease severity scores used for UC and CD.

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

CCI [redacted]

10.2.1.4 Reporting Special Interest AEs

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

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

Subjects and parents/legal guardians should be instructed to report symptoms, such as the development of rash, hives, pruritus, flushing, urticaria, that may represent an infusion-related reaction to study drug. If signs or symptoms of an infusion-related reaction are observed during the administration of study drug, it should be immediately discontinued and the subject treated as medically appropriate. In the case of a mild reaction, study drug administration may be reinitiated (with appropriate premedication) at the discretion of the investigator. Subjects with severe or serious infusion-related reactions (eg, stridor, angioedema, life-threatening change in vital signs) must be withdrawn from the study.

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

Serious Infection

Subjects will be monitored for signs and symptoms of infection and for lymphopenia during the study. Subjects with signs and symptoms suggestive of infections, including GI infections, will be treated as clinically indicated. Interventions may include antibiotic treatment, if appropriate and/or discontinuation of concomitant immunomodulators. Blood, sputum, urine, and/or stool cultures should be obtained as appropriate for the detection and diagnosis of infection. Withholding or terminating study drug administration may be considered, as described in Section 7.5.

Subjects and caregivers will be advised to seek medical attention for potential serious infection if they have signs and/or symptoms including, but not limited to, acute change in level of consciousness, high or low temperature (>38.5°C or <36°C), fast heart beat (tachycardia >140 beats per minutes [bpm] for ages 2 to 5 years, >130 bpm for ages 6 to 12 years, >110 bpm for ages 13 to 18 years), difficult or rapid breathing (respiratory rate >22/min for ages 2 to 5 years, >18 for ages 6 to 12 years, >14 for ages 13 to 18 years), passing out/faintness, drowsiness/difficult to rouse, unusual irritability, poor feeding/eating/drinking, seizure, and acute or dramatic increase in pain.

Malignancy

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

Other

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

10.2.2 Collection and Reporting of SAEs

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

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

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

The SAE eCRF should be transmitted 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 the attention of the contact listed in Section 1.1.

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

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

10.2.3 Reporting of Abnormal LFTs

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

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

10.2.4 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. An investigator who is made aware of or identifies a potential product complaint 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.

10.3 Follow-up of SAEs

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

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports 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 study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Data Safety Monitoring Board

An independent DSMB has been established to review safety, PK, and other relevant data, and to monitor the general safety of subjects who participate in the study.

The DSMB will have scheduled regular meetings performing a full safety assessment to ensure monitoring of the overall safety of the study subjects. In addition, ad hoc meetings can be requested at any time by Takeda and the DSMB.

The composition of, and working procedures for the DSMB are defined in the DSMB Charter and will be provided to the DSMB members. The DSMB charter is not included in this protocol.

11.2 Adjudication Committee

A PML 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.

11.2.1 Risk Assessment and Management Program 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 and typically only occurs in patients who are immunocompromised [31,32]. Natalizumab is a pan-α_4 integrin antagonist that binds to both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins and inhibits cellular adhesion to vascular cell adhesion molecule-1(VCAM-1) and MAdCAM-1 [33,34]. In contrast, vedolizumab binds to the $\alpha_4\beta_7$ integrin only [27] and inhibits adhesion to MAdCAM-1, but not VCAM-1. Although no cases of PML have been reported in clinical studies with vedolizumab to date, a risk of PML cannot be ruled out.

To address the theoretical risk of the development of PML in subjects treated with vedolizumab, the sponsor, with input from renowned PML experts, has developed a Risk Assessment and Management Program for PML (RAMP) for PML. The complete description of the RAMP program, including materials and instructions for its implementation and monitoring, is included in the study manual.

The RAMP is focused on early clinical detection and management of that specific safety risk, including the discontinuation of study drug, if applicable. Subjects are assessed for signs and symptoms of PML prior to the administration of each dose of study drug using a PML subjective symptom checklist. Subjects with a positive PML subjective symptom checklist at any time after enrollment in a vedolizumab clinical study will be evaluated according to a prespecified algorithm (the PML Case Evaluation Algorithm), which may include evaluation by a neurologist as appropriate. 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/parents/legal guardians will be trained to report specific neurological signs and symptoms without delay. Educational materials for teaching site personnel and subjects/parents or legal guardians about PML and the RAMP procedures will be distributed to all sites and are included in the study manual. Formal teaching and training will be performed for site personnel prior to the start of the study. Subjects will receive age-appropriate educational materials prior to receiving treatment. The informed consent form will contain specific information on the hypothetical risk of PML. Any documented case of PML will be reported as an SAE, regardless of whether hospitalization occurs.

12.0 DATA HANDLING AND RECORD KEEPING

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

12.1 eCRFs

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

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

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

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

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the study sponsor or its designee. 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/assent 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 receiving unblinding of subject's treatment assignment from IRT after database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

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

13.1.1 Analysis Sets

The full analysis set (FAS) will include all randomized subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to treatment they were randomized to receive.

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

The PK set is defined as all subjects who receive at least 1 dose of study drug and have at least 1 measurable concentration of vedolizumab.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose group and overall based on all randomized subjects. Additional summaries will be provided for the FAS and other analysis sets, as appropriate. For continuous variables, summary statistics (nonmissing values, mean, median, SD, minimum and maximum) will be generated. For categorical variables, the counts and percentages of each possible value will be generated.

Medical history will be summarized by system organ class and preferred term. Medication history and concomitant medications will be summarized by preferred name.

13.1.3 Efficacy Analysis

All proportion-based efficacy endpoints will be summarized by presenting the point estimate and 95% CIs for the proportion by indication (UC or CD) and weight groups. For all subjects with missing Mayo, CDAI, PUCAI, or PCDAI data for determination of endpoint at any time point, to ensure all subjects in the FAS are included in the analysis, a subject with any component of a scale missing will be considered to be a nonresponder/nonremitter for that particular endpoint, scale, and time point. Change from Baseline in fecal calprotectin results will be summarized by weight group.

13.1.4 PK Analysis

Measured serum concentrations of vedolizumab by time will be summarized by dose and weight groups using descriptive statistics. Individual serum concentration data versus time will be presented by dose group in a data listing.

The PK parameters will be derived by compartmental and/or noncompartmental approaches, data permitting. The Clinical Pharmacology Data Analysis Plan and SAP will provide further details of derivations. All PK parameters will be summarized using descriptive statistics (nonmissing values, mean, SD, percent coefficient of variation, median, minimum, maximum) by dose and weight group. In addition, $C_{trough,Wk\ 14}$ will be summarized using descriptive statistics by dose, weight group, and by response status based on complete Mayo score or CDAI.

Further analysis will be performed as deemed necessary and will not be reported in the clinical study report. These analyses will be part of a separate report.

13.1.5 Other Analyses

The dose-response relationship at Week 14 will be explored. Further details will be provided in the SAP.

Change from Baseline in IMPACT-III total and subscale scores will be summarized descriptively by dose group.

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[redacted]

13.1.6 Safety Analysis

Safety analyses will be performed using the safety analysis set. Safety data will be summarized by dose group and various subgroups including by indication (UC or CD) and weight group. No statistical inference will be made for safety analyses.

The number and percentage of subjects with TEAEs (defined as any AE, regardless of relationship to study drug), AESIs (ie, malignancies, infusion reactions, serious infections, liver injury, PML), 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. Separate summaries will also be generated for TEAEs overall and by severity.

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

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

13.2 Interim Analysis

Several interim analyses will be conducted to support future pediatric studies. These interim analyses may occur 1) when at least 20 patients in either weight group have completed Week 22 or withdrawn from the study or 2) when all subjects per indication and weight group (ie, UC 10 kg to <30 kg, CD 10 kg to <30 kg, UC ≥30 kg, CD ≥30 kg) have completed the study. Interim analyses will be carried out by an independent statistical group not involved in daily activities of the study.

13.3 Determination of Sample Size

The planned sample size is 80 subjects including 40 subjects who weigh ≥30 kg and 40 subjects who weigh 10 kg to <30 kg. Subjects will be randomly assigned in a 1:1 ratio to receive 1 of 2 dose regimens (high or low) per weight group per weight group (≥30 kg or 10 kg to <30 kg). The randomization will be stratified by previous exposure/failure to TNF-α antagonist therapy or naive to TNF-α antagonist therapy and by indication (UC or CD) and by weight group (≥30 kg or 10 kg to <30 kg). Randomization caps will be implemented to ensure that the sample size for each dose regimen will be a minimum of 9 subjects with UC and 9 subjects with CD per weight group. A sample size of 9 subjects is expected to have at least 80% power to establish 95% CIs that are within 60% and 140% of the geometric mean estimates for CL for each dose (high or low), indication (UC or CD), and weight group (≥30 kg or 10 kg to <30 kg), assuming the intersubject variability for CL in the pediatric population is similar to that in the adult population (%CV ≤36.6%). The sample size is based on industry guidance [35,36]; CL is used because it controls overall drug exposure (AUC and average serum concentration during a dosing interval) and it is the parameter that allows computation of the dosage required to maintain an average steady-state concentration. The proposed sample size will also allow for descriptive analysis of efficacy for each indication and characterization of the dose-response relationship in pediatric subjects.

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 in the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

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

14.2 Protocol Deviations

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

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

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and 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 requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification from the sponsor or designee, 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/assent 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/assent 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/assent 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/assent is given. The informed consent/assent 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/assent form and if applicable, the subject authorization form. The informed consent/assent 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/assent 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/assent 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/assent, then the subject's legally acceptable representative may provide such consent/assent 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/assent 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/assent form and subject authorization (if applicable) at the time of consent/assent 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/assent 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 or the subject's legally acceptable representative signs the informed consent/assent in the subject's medical record. Copies of the signed informed consent/assent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject or the subject's legally acceptable representative.

All revised informed consent/assent 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/assent was obtained should be recorded in the subject's medical record, and the subject or the subject's legally acceptable representative should receive a copy of the revised informed consent/assent 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, 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

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 the investigators' city, state (for investigators in the United States), 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

	Days -28 to -1	Day 1	Wk 1	Wk 2	Wk 2-6*	Wk 6	Wk 10	Wk 14	Wk 22 End-of-Study/ ET Visit (a)	Unscheduled Visit (UC/CD Exacerbation or Other) (b)	Wk 32 (or last dose day +18 weeks) Final Safety Visit (a)
Visit Windows:	NA	NA	± 2 days	± 2 days	NA	±3 days	±3 days	±3 days	±3 days		±1 wk
Visit Day		1	8	15	16-42	43	71	99	155		
Visit Number:	1	2	3	4	5	6	7	8	9		10
Informed consent/pediatric assent	X										
PML wallet card	X										
Allergy reaction card	X										
Demographics	X										
Medical history	X										
Medication history	X										
UC/CD prior biologics history	X										
Dosing (see Figure 6.a)		X		X		X		X			
Physical examination (c)	X	X		X		X	X	X	X	X	X
Weight and height (d)	X	X		X		X	X	X	X	X	X
Vital signs (e)	X	X		X		X	X	X	X	X	X
PML checklist (f)	X	X		X		X		X	X	X	X
Concomitant medications	X (g)	X	X	X	X	X	X	X	X	X	X
Concomitant procedures	X (g)	X	X	X	X	X	X	X	X	X	X
IRT Randomization/drug dispensing		X		X		X		X			
PUCAI/PCDAI (h)	X	X		X		X	X	X	X	X	
Complete Mayo (UC subjects only) (i)	X							X	X		
Partial Mayo (UC subjects only) (i)		X		X		X	X		X	X	
CDAI score	X (j)	X		X		X	X	X	X	X	
Endoscopy (k)	X							X	X		
Subject diary dispensed (l)	X	X	X	X		X	X	X	X		
TB screening	X										

Footnotes on next page.

Appendix A Schedule of Study Procedures (continued)

	Days -28 to -1	Day 1	Wk 1	Wk 2	Wk 2-6*	Wk 6	Wk 10	Wk 14	Wk 22 End-of-Study/ ET Visit (a)	Unscheduled Visit (UC/CD Exacerbation or Other) (b)	Wk 32 (or last dose day +18 weeks) Final Safety Visit (a)
Visit Windows:	NA	NA	± 2 days	± 2 days	NA	±3 days	±3 days	±3 days	±3 days		±1 wk
Visit Day		1	8	15	16-42	43	71	99	155		
Visit Number:	1	2	3	4	5	6	7	8	9		10
Stool sample for culture (m)	X									X	
Fecal calprotectin (n)	X							X	X	X	
PTE assessment (o)	X	X									
AE assessment (p)		X	X	X	X	X	X	X	X	X	X
Sample collection for:											
Serum pregnancy test (q)	X								X		
Urine pregnancy test (q)		X		X		X		X		X	
HBV, HCV, HIV screening	X										
Clinical chemistry (including CRP)	X	X		X		X	X	X	X	X	X
Hematology (r)	X	X		X		X	X	X	X	X	X
PK assessment (s)		X	X	X	X	X	X	X	X	X	X
CCI											
IMPACT-III (u)		X							X		

* Wk 2-6=nondosing visit scheduled anytime between Days 16 and 42 for PK collection.
CRP=C-reactive protein, NA=not applicable.
(a) Subjects discontinued from the study for any reason will complete procedures for Week 22/ET assessments (plus fecal calprotectin sample, and endoscopy and Complete Mayo Score if before Week 14 Visit), the Final Safety Visit (18 weeks after the last dose of study drug), and will also be contacted by telephone 6 months after the last dose of study drug to complete a long-term follow-up safety survey. Subjects who complete the study but do not enter the extension study will complete procedures for Week 22 assessments (but will not repeat fecal calprotectin sample, or endoscopy and Complete Mayo Score performed at the Week 14 Visit), the Final Safety Visit (18 weeks after the last dose of study drug [Week 32]), and will also be contacted by telephone 6 months after the last dose of study drug to complete a long-term follow-up safety survey.
(b) Subjects seen at an unscheduled visit for disease exacerbation will complete all of the Unscheduled Visit assessments. Other unscheduled visits may include concomitant medications, vital signs, clinical laboratory blood draws, urine sample, and AE collection, as appropriate.
(c) Physical examination: clinically significant findings will be recorded as Medical History if start is prior to signing the informed consent/pediatric assent, as PTEs if start is after signing of the informed consent/pediatric assent, or as AEs if start is after the first dose of study drug.
(d) Weight (kg; without shoes, socks, or hats) and height (cm) will be measured during Screening and study visits per table above. Weight should be measured prior to dosing on Day 1 and Weeks 2, 6, and 14.
(e) Vital signs should be measured prior to dosing on Day 1 and Weeks 2, 6, and 14 or at any time at visits when study drug is not administered per table above.
(f) Must be performed at Screening and prior to dosing on Day 1 and Weeks 2, 6, and 14.

(g) Monitoring of concomitant medications and concomitant procedures will begin at signing of the informed consent/pediatric assent.
(h) The components of the PUCAI/PCDAI scores may be completed within 7 days prior to receiving study drug.
(i) A complete Mayo score is required when endoscopy is performed. A complete Mayo score will be obtained within 28 days prior to randomization to determine eligibility (an endoscopy performed prior to consent/pediatric assent if within 28 days prior to signing of informed consent/assent is also acceptable). A baseline complete Mayo score, calculated by adding the screening endoscopy subscore to the partial Mayo score obtained on Day 1 (or within 28 days prior to signing of informed consent/assent if applicable), will be used for the comparison with the Week 14 complete Mayo score to determine response at Week 14. A complete Mayo score will be obtained for subjects who withdraw prior to Week 14 if they undergo endoscopy at the ET Visit.
(j) The subcomponents of the CDAI score will be completed within 7 days prior to randomization using hematocrit results collected during Screening.
(k) Endoscopy will be performed during Screening unless 1 has already been performed within 28 days prior to signing of informed consent/assent. The endoscopy at Week 22/ET is only required for ET visits that occur prior to Week 14. An ET endoscopy is not required if a subject withdraws prior to Week 6.
(l) The subject diaries will be dispensed at each visit and completed daily for CD subjects and UC subjects. Three days (UC) or 5 days (CD) of completed diary data prior to the Day 1 visit is required for disease activity index calculation. Diary entries preceding each subsequent study visit (7 day for UC and 10 days for CD) will be used to calculate the Mayo or CDAI score. Because the flexible sigmoidoscopy/colonoscopy preparation can interfere with the assessment of other clinical parameters, diary entries used to calculate the complete Mayo or CDAI score should not be from days during which the flexible sigmoidoscopy/colonoscopy preparation is administered.
(m) A stool sample will be obtained for culture, ova and parasite evaluation, and *C difficile* assay. A sample will be collected and cultured during Screening and at any point in the study when a subject becomes symptomatic, including worsening of UC or CD.
(n) A stool sample will be collected during Screening, Week 14, and at unscheduled visits due to disease exacerbations for the analysis of fecal calprotectin. The stool sample for the analysis of fecal calprotectin must be collected before any bowel preparation is given and before dosing. A stool sample should be collected at the ET Visit for subjects who withdraw before Week 14, but is not to be collected at the Week 22/End-of-Study Visit for subjects who completed the procedure at Week 14.
(o) PTEs will be captured immediately following the signing of the informed consent/pediatric assent at Screening, up until the first dose of study drug.
(p) Collection of all AEs will commence from the time that the subject is first administered study drug and will continue through Week 22 for subjects who enter the extension study or the Final Safety Visit (18 weeks after the last dose of study drug) for subjects who do not enter the extension study.
(q) All female subjects of childbearing potential (females who reach menarche prior to or during the study) (as per Section 9.1.11) must have a serum pregnancy test at Screening and Week 22/ET visit. A urine pregnancy test will be completed for all females of childbearing potential prior to each dose of study drug (Day 1 and Weeks 2, 6, and 14), and at any unscheduled visit.
(r) The ESR may be performed at a local laboratory.
(s) The exact time of blood draw must be accurately registered in the eCRF. PK samples will be collected on Day 1 (1 sample: postdose); Day 8 [Wk 1] (1 sample); Days 15 [Wk 2], 43 [Wk 6], and 99 [Wk 14] (2 samples predose and postdose); any time between Days 16 and 42 [Wks 2-6] (1 sample); Day 71 [Wk 10] (1 sample), Day 155 [Wk 22] (1 sample), and Final Safety Visit 18 weeks after the last dose of study drug (1 sample postdose of final administration for subjects who ET or for subjects who do not enroll in the extension study). The postdose samples collected on dosing days should be collected as close to the end of infusion as feasible (and must be obtained within 60 minutes after the end of the infusion) from the opposite arm in which the study drug infusion was given. If blood collection from the opposite arm in which the study drug infusion was given is not feasible, the postdose sample may be collected from the infusion arm 30 to 60 minutes after the end of infusion and after the IV saline flush has been completed.
(t) CCI [redacted]
(u) IMPACT-III (where translations are available) will be administered to subjects aged 9 to 17 years.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study related duties and functions and should implement procedures to ensure the integrity of the study related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or

that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject or subject's legal representative:

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 or the subject's legally acceptable representative otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent)

from Screening throughout the duration of the study and for 18 weeks after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study and for 18 weeks after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E PUCAI

The PUCAI is composed of 6 clinical items. Weights of the included items were assigned according to a multivariate regression analysis of 157 children with UC, in which rectal bleeding assumed the highest weight.

The historical parameters should reflect a daily average of the patient's last 48 hours. However, if the patient's condition is changing rapidly, the last 24 hours may be used. The PUCAI score ranges from 0 to 85; a score of <10 denotes remission, 10 to 34 mild disease, 35 to 64 moderate disease, and 65 to 85 severe disease. A clinically significant response is defined as a PUCAI change of ≥20.

	Item	Points
1	**Abdominal pain**	
	no pain	0
	pain can be ignored	5
	pain cannot be ignored	10
2	**Rectal bleeding**	
	none	0
	small amount only, in <50% of stools	10
	small amount with most stools	20
	Large amount	30
3	**Stool consistency of most stools**	
	Formed	0
	Partially formed	5
	Completely unformed	10
4	**Number of stools per 24 hours**	
	0-2	0
	3-5	5
	6-8	10
	>8	15
5	**Nocturnal stools (any episode causing wakening)**	
	No	0
	Yes	10
6	**Activity level**	
	No limitation of activity	0
	Occasional limitation of activity	5
	Severe restricted activity	10
	SCORE	**Total Max 85**

Appendix F Mayo Scoring System for the Assessment of Ulcerative Colitis Activity

Category (a)
Stool frequency (b)
0=Normal no. of stools for this patient
1=1 to 2 stools more than normal
2=3 to 4 stools more than normal
3=5 or more stools more than normal
Subscore, 0 to 3
Rectal bleeding (c)
0=No blood seen
1=Streaks of blood with stool less than half the time
2=Obvious blood with stool most of the time
3=Blood alone passes
Subscore, 0 to 3
Findings on endoscopy
0=Normal or inactive disease
1=Mild disease (erythema, decreased vascular pattern, mild friability)
2=Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3=Severe disease (spontaneous bleeding, ulceration)
Subscore, 0 to 3; 0=Normal or inactive disease
Physician's global assessment (d)
0=Normal
1=Mild disease
2=Moderate disease
3=Severe disease
Subscore, 0 to 3

Source: Adapted from Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317(26):1625-9.
(a) The Mayo score ranges from 0-12, with higher scores indicating more severe disease. Partial Mayo score excludes endoscopy and ranges from 0-9.
(b) Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
(c) The daily bleeding score represents the most severe bleeding of the day.
(d) The physician's global assessment acknowledges the 3 other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Appendix G PCDAI

The PCDAI was specifically designed for use in children. The PCDAI includes a child-specific item: the height velocity variable as well as 3 laboratory parameters: hematocrit (adjusted for age and sex), ESR, and albumin level.

The limitation of activity should be based on the most significant limitation during the past week, even if it is only for 1 day. However, if the activity limitation is due to another illness (eg, upper respiratory infection), the illness period should be excluded from the patient's PCDAI score.

The PCDAI score can range from 0-100, with higher scores signifying more active disease. A score of <10 is consistent with inactive disease, 11 to 30 indicates mild disease, and >30 is moderate-to-severe disease. A decrease of 12.5 points is taken as evidence of improvement.

History (recall 1 week)				
Abdominal pain				
None				0
Mild (brief episodes, not interfering with activities)				5
Moderate/severe (frequent or persistent, affecting activities)				10
Stools				
0-1 liquid stools, no blood				0
2-5 liquid or up to 2 semi-formed with small blood				5
Gross bleeding, >6 liquid stools or nocturnal diarrhoea				10
Patient functioning, general well-being (Recall, 1 week)				
No limitation of activities, well				0
Occasional difficulties in maintaining age appropriate activities, below par				5
Frequent limitation of activities, very poor				10
EXAMINATION				
Weight				
Weight gain or voluntary weight loss				0
Involuntary weight loss 1-9%				5
Weight loss >10%				10
Height				
<1 channel decrease (or height velocity >-SD)				0
>1<2 channel decrease (or height velocity <-1SD>-2SD)				5
>2 channel decrease (or height velocity <-2SD)				10
Abdomen				
No tenderness, no mass				0
Tenderness, or mass without tenderness				5
Tenderness, involuntary guarding, definite mass				10
Peri-rectal disease				
None, asymptomatic tags				0
1-2 indolent fistula, scant drainage, tenderness of abscess				5
Active fistula, drainage, tenderness or abscess				10
Extra-intestinal manifestations (Fever >38.5 x 3 days in week, arthritis, uveitis, erythema nodosum, or pyoderma gangrenosum)				
none				0
one				5
two				10
LABORATORY				
Hematocrit (%)				
<10 years	11-14 (male)	11-19 (female)	15-19 (male)	
>33	>35	>34	>37	0
28-33	30-34	29-33	32-36	2.5
<28	<30	<29	<32	5
ESR (mm/hr)				
<20				0
20-50				2.5
>50				5
Albumin (g/L)				
>35				0
31-34				5
<30				10

Appendix H CDAI Scoring System for the Assessment of CD Activity

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

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

Appendix I SES-CD

	SES Score			
Variable	**0**	**1**	**2**	**3**
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter ≥2)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD=sum of all variables for the 5 bowel segments.
Values are given to each variable for every examined bowel segment.
Source: Adapted from Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60(4):505-12.

Appendix J Summary of Changes

Change 1: Clarified procedures for completion and review of entries to diaries.

The primary change occurs in Section 9.1.6.1 Completion and Review of Entries to Diaries

Initial wording:	9.1.6.1 Completion and Review of Entries to Diaries During Screening, subjects and parents or legal guardians will be instructed on how to appropriately complete entries into the diary. Three days (UC) or 5 days (CD) of completed diary data prior to the Day 1 visit is required for disease activity index calculation.
Amended or new wording:	9.1.6.1 Completion and Review of Entries to Diaries During Screening, subjects and parents or legal guardians will be instructed on how to appropriately complete entries into the diary. Three days (UC) or 5 days (CD) of completed diary data prior to the Day 1 visit is required for disease activity index calculation. **Data on disease activity collected during screening will be reviewed on Day 1, before administering the first dose of study drug to ensure that the subject is still eligible for inclusion. Scores between initial screening and Day 1 before dosing should not change substantially.**

Rationale for Change:

Amended to ensure that eligibility for the study is maintained at the end of the screening period.

Change 2 Clarification of criteria for interim analysis.

The primary change occurs in Section 13.2 Interim Analysis:

Initial wording:	Several interim analyses will be conducted to support future pediatric studies. These will occur 1) when 20 patients in the ≥30 kg weight group have completed Week 22 or withdrawn from the study and 2) when all subjects per indication and weight group (ie, UC 10 kg to <30 kg, CD 10 kg to <30 kg, UC ≥30 kg, CD ≥30 kg) have completed the study. Interim analyses will be carried out by an independent statistical group not involved in daily activities of the study.
Amended or new wording:	Several interim analyses will be conducted to support future pediatric studies. These ~~will~~ **interim analyses may** occur 1) when **at least** 20 patients in ~~the ≥30 kg~~ **either** weight group have completed Week 22 or withdrawn from the study ~~and~~ or 2) when all subjects per indication and weight group (ie, UC 10 kg to <30 kg, CD 10 kg to <30 kg, UC ≥30 kg, CD ≥30 kg) have completed the study. Interim analyses will be carried out by an independent statistical group not involved in daily activities of the study.

Rationale for Change:

Amended to make provision for interim analyses in both weight groups (ie, the <30 kg group as well as the previously planned ≥30 kg group) before all subjects have completed Week 22 or were withdrawn from the study.

Change 3: Amended the concomitant oral corticosteroid dosing information.

The primary change occurs in Section 7.3.1.1 Oral Corticosteroid Dosing:

Initial wording:

…

- For subjects entering the study at a corticosteroid dose of <20 mg/day, tapering may resume by 5 mg/week down to 10 mg/day for those who weigh ≥40 kg or more and down to 0.25 mg/day for those weighing <40 kg.

Once these thresholds are reached, the corticosteroid dose will be held stable until the third dose of study drug is given at Week 6. Thereafter, between Weeks 6 and 14, corticosteroid tapering may resume at the discretion of the investigator by 5 mg/week down to 10 mg/day, and thereafter by 2.5 mg/wk until zero.

Amended or new wording:

…

- For subjects entering the study at a corticosteroid dose of <20 mg/day, tapering may resume by 5 mg/week down to 10 mg/day for those who weigh ≥40 kg or more and down to 0.25 mg/**kg**/day for those weighing <40 kg.

Once these thresholds are reached, the corticosteroid dose will be held stable until the third dose of study drug is given at Week 6. Thereafter, between Weeks 6 and 14, corticosteroid tapering may resume at the discretion of the investigator by 5 mg/week down to 10 mg/day, and thereafter by 2.5 mg/w**ee**k until zero.

Rationale for Change:

To correct dosages for corticosteroid tapering in subjects entering the study at a dose of <20 mg/day.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	05-Sep-2019 15:35 UTC
	Clinical Science Approval	06-Sep-2019 01:51 UTC
	Biostatistics Approval	06-Sep-2019 20:44 UTC